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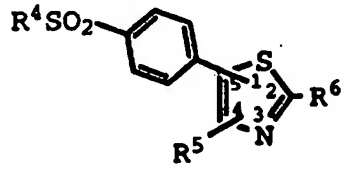
(54) Title: SUBSTITUTED THIAZOLES FOR THE TREATMENT OF INFLAMMATION

(57) Abstract

A class of substituted thiazolyl compounds is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by Formula (II), wherein R^4 is selected from alkyl and amino, wherein R^5 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aminosulfonyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, heterocyclic and nitro; and wherein R^6 is selected from halo, amino, alkoxy, nitro, hydroxyl, aminocarbonyl, acyl, alkylaminocarbonyl, arylaminocarbonyl, alkenyl, alkynyl, haloalkoxy, alkylamino, arylamino, aralkylamino, alkoxycarbonylalkyl, alkylaminoalkyl, heterocycloalkyl, aralkyl, cyanoalkyl, N-alkylsulfonylamino, heteroarylsulfonylalkyl, heteroarylsulfonylhaloalkyl, aryloxyalkyl, aralkyloxyalkyl, aryl and heterocyclo, wherein the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, haloalkyl, haloalkoxy, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, amino, acyl and alkylamino; or a pharmaceutically-acceptable salt thereof.



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SUBSTITUTED THIAZOLES FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces

inflammation and produces fewer and less drastic side effects.

The references below that disclose antiinflammatory activity, show continuing efforts to find a safe and effective antiinflammatory agent. The novel thiazoles disclosed herein are such safe and also effective antiinflammatory agents furthering such efforts. The invention compounds are found to show usefulness *in vivo* as antiinflammatory agents with minimal side effects. The substituted thiazoles disclosed herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

U.S. Patent No. 5,232,921 to Biziere et al. describes 2-alkylaminothiazoles as having an affinity for muscarinic cholinergic receptors.

PCT application WO 93/15071, published Aug. 5, 1993, describes 4-(2-pyridyl)thiazole derivatives as inhibiting gastric acid secretion. Specifically, 2-(phenylmethyl)-4-(2-pyridyl)-5-(2-methylphenyl)thiazole is described. U.S. Patent No. 4,612,321 to S. Terao and Y. Maki describes 5-pyridylthiazole derivatives, and specifically 5-pyridyl-4-(4-methoxyphenyl)-2-thienylthiazole, as having antiinflammatory activity.

U.S. Patent No. 4,659,726 to Yoshino et al., describes 4,5-bis(4-methoxyphenyl)-2-(2-pyrrolyl)thiazoles as being effective as platelet aggregation inhibitors. U.S. Patent No. 5,217,971 to Takasugi et al. describes 4,5-diphenylthiazole compounds as having antiinflammatory properties, and specifically 4,5-bis(4-methoxyphenyl)-2-(4-pyridyl)thiazole.

U.S. Patent No. 4,168,315 to R. Rynbrandt and E. Nishizawa describes 4,5-diphenylthiazole derivatives as being blood platelet agglutination inhibitors. U.S. Patent No. 4,322,428 to K. Matsumoto and P. Ho, describe 2-(4-halophenyl)-4,5-bis(4-methoxyphenyl)thiazoles as being antiinflammatory. U.S.

Patent No. 4,451,471 to P. Ferrini and R. Göschke describes 2-thio-4,5,diarylthiazole derivatives as having antiinflammatory activity. 4,5-Bis(4-methoxyphenyl)thiazole is described as a synthetic intermediate. PCT application WO 87/6429, published Nov. 5, 1987, describes thienylthiazole compounds, and specifically 4-(4-chlorophenyl)-2-(5-chloro-2-thienyl)-5-(4-methylphenyl)thiazole, as having insecticidal utility.

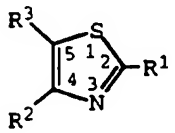
U.S. Patent No. 4,051,250 to Dahm et al. describes 4,5-diarylthiazole compounds as being antiinflammatory. Specifically, 2-chloro-4-(4-chlorophenyl)-5-(4-methylmercaptophenyl)thiazole is described as a synthetic intermediate. European Application EP 592,664, published April 20, 1994, describes 4,5-diphenylthiazoles as having antiinflammatory activity, and specifically 4-[4-(methylsulfonyloxy)phenyl]-5-phenyl-2-[bis(N-methylsulfonyl)amino]thiazole. Seko et al. [*Chem. Pharm. Bull.*, **39**, 651 (1991)] describe the platelet aggregation and cyclooxygenase inhibitory activity of 4,5-diphenylthiazoles, and specifically of 4,5-bis(4-methylthiophenyl)-2-(1,5-dimethyl-2-pyrrolyl)thiazole. Japanese application 4,244,073 describes thiazole compounds for the treatment of thrombosis.

PCT application, WO 95/00501, published January 5, 1995, describes substituted thiazoles as antiinflammatories. Japanese application JP 4,173,782 describes 2-haloalkylsulfonamide-4,5-diphenylthiazole derivatives as having antiinflammatory activity.

U.S. Patent No. 4,632,930 to D. Carini and R. Wexler describes alkylaryl thiazole derivatives, and specifically 5-phenyl-4-(methylsulfonylphenyl)-α,α-bis(trifluoromethyl)thiazole-2-methanol, as having antihypertensive properties.

DESCRIPTION OF THE INVENTION

A class of substituted thiazolyl compounds useful in treating inflammation and inflammation-related disorders is defined by Formula I:



I

wherein R^1 is selected from hydrido, halo, amino, alkoxy, cyano, nitro, hydroxyl, aminocarbonyl, acyl, alkylaminocarbonyl, arylaminocarbonyl, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, carboxyl, carboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylaminoalkyl, heterocycloalkyl, aralkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, N-alkylsulfonylamino, heteroarylsulfonylalkyl, heteroarylsulfonylhaloalkyl, aryloxyalkyl, aralkyloxyalkyl, aryl and heterocyclo, where the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, haloalkyl, haloalkoxy, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, amino, acyl and alkylamino; and

wherein R^2 and R^3 are independently selected from alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^2 and R^3 are optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aminosulfonyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, alkoxyalkyl,

hydroxyalkyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, heterocyclic and nitro;

provided one of R^2 and R^3 is aryl substituted with alkylsulfonyl, haloalkylsulfonyl or aminosulfonyl; further provided that R^2 is not 4-fluorophenyl when R^1 is methyl and R^3 is 4-methylsulfonylphenyl; further provided that R^3 is not 4-fluorophenyl when R^1 is methyl and R^2 is 4-aminosulfonylphenyl; further provided R^2 and R^3 are not phenyl substituted with α,α-bis(methyl)methanol; and further provided that R^2 is not 4-(methylsulfonyl)phenyl when R^1 is α,α-bis(trifluoromethyl)methanol;

or a pharmaceutically-acceptable salt thereof.

The phrase "further provided", as used in the above description, is intended to mean that the denoted proviso is not to be considered conjunctive with the other provisos.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the

prevention of colorectal cancer. Compounds of the invention would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds were also be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis, and of acute injury to the eye tissue. The compounds would also be useful for the treatment of certain central nervous system disorders such as Alzheimer's disease and dementia. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma.

Besides being useful for human treatment, these compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

Suitable LTB_4 inhibitors include, among others, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688,

Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the LTB_4 inhibitors are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

Suitable 5-LO inhibitors include, among others, masoprocol, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate, and bunaprolast.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} equal to or less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1.0 μM, and more preferably of greater than 10 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

A preferred class of compounds consists of those compounds of Formula I wherein R^1 is selected from hydrido, halo, amino, lower alkoxy, cyano, nitro, hydroxyl, aminocarbonyl, acyl, lower alkylaminocarbonyl, phenylaminocarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, phenylamino, lower aralkylamino, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminoalkyl, lower heterocycloalkyl, lower aralkyl, lower cyanoalkyl, lower N-alkylsulfonylamino,

lower heteroarylsulfonylalkyl, lower heteroarylsulfonylhaloalkyl, lower aryloxyalkyl, lower aralkyloxyalkyl, aryl and heterocyclo, wherein the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino; and wherein R^2 and R^3 are independently selected from lower alkyl, lower alkenyl, aryl, lower cycloalkyl, lower cycloalkenyl and heterocyclic; wherein R^2 and R^3 are optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkenyl, lower alkynyl, cyano, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, acyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, heterocyclic and nitro; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is selected from fluoro, chloro, bromo, iodo, amino, methoxy, ethoxy, propoxy, butoxy, isopropoxy, *tert*-butoxy, cyano, nitro, hydroxy, aminocarbonyl, formyl, acetyl, N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methyl-N-phenylaminocarbonyl, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, ethylenyl, propylenyl, butenyl, pentenyl, isopropylenyl, isobutylenyl, propargyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl,

difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, N-methylamino, N-ethylamino, N-propylamino, N-butylamino, N-*tert*-butylamino, N-pentylamino, N-hexylamino, N,N-dimethylamino, carboxyl, N-benzylamino, 3,5-dichlorophenylamino, 3,5-dichlorophenoxymethyl, 3-chlorophenoxymethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, methylaminomethyl, morpholinomethyl, pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, pyridylmethyl, thienylmethyl, benzyl, phenethyl, phenylpropyl, cyanomethyl, phenoxymethyl, benzyloxymethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, N-methylsulfonylamino, (2-thienyl)sulfonylmethyl, (2-thienyl)sulfonylbromomethyl, phenyl optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, methoxy, ethoxy, propoxy, butoxy, isopropoxy, *tert*-butoxy, methylthio, methylsulfinyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, amino, formyl, methylamino and dimethylamino, and heterocyclic selected from morpholino, pyrrolidinyl, piperazinyl, piperidinyl, pyridyl, thienyl, thiazolyl, oxazolyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, imidazolyl, and benzimidazolyl, furyl, pyrrolyl, pyrazolyl and triazolyl, optionally substituted at a substitutable position with one or more radicals

selected from fluoro, chloro, bromo, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, methoxy, ethoxy, propoxy, butoxy, isopropoxy, *tert*-butoxy, methylthio, methylsulfinyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, amino, formyl, methylamino and dimethylamino; and wherein R^2 and R^3 are independently selected from methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, ethylenyl, propylenyl, butenyl, pentenyl, isopropylenyl, isobutylenyl, phenyl, naphthyl, biphenyl, pyridyl, thienyl, thiazolyl, oxazolyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolinyl, imidazolyl, benzimidazolyl, furyl, pyrrolyl, pyrazolyl, triazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, morpholino, pyrrolidinyl, piperazinyl and piperidinyl; wherein R^2 and R^3 are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, ethylenyl, propylenyl, butenyl, pentenyl, isopropylenyl, isobutylenyl, propargyl, cyano, carboxyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, formyl, acetyl, N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methyl-N-phenylaminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,

heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, ethoxy, propoxy, butoxy, isopropoxy, *tert*-butoxy, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, pyridyl, furyl, pyrazinyl, pyrrolyl, pyrazolyl, morpholino, pyrrolidinyl, piperazinyl, piperidinyl, triazolyl and nitro; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-phenylthiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-methoxyphenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-chlorophenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(N-hexylamino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(N-methylamino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(N-ethylamino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(N-tert-butylamino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(N-(4-phenoxyphenyl)amino)thiazole;

ethyl 4-[[5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]amino]benzoate;

ethyl 3-[[5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]amino]benzoate;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(2-phenylethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(N-(3,5-dichlorophenyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(N-butylamino)thiazole;

4-[5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]aminobenzoic acid;

3-[5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]aminobenzoic acid;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-ethylthiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3-phenylpropyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-chlorophenoxy)methyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(2-methyl-4-thiazolyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(2-fluorophenyl)-2-(2-chlorophenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(2,5-difluorophenyl)-2-(2-chlorophenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(2,3,4,5,6-pentafluorophenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((2-chlorophenoxy)methyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-bromophenyl)-2-(2-chlorophenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(2-fluorophenyl)-2-((3-chlorophenoxy)methyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-dichlorophenoxy)methyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(2-fluorophenyl)-2-((4-methoxyphenoxy)methyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-bromophenyl)-2-(2-chlorophenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-methylthiophenyl)-2-(2-chlorophenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(3-fluoro-4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(3-chloro-4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(3-chloro-4-methylphenyl)-2-(2-chlorophenyl)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(3-methyl-4-chlorophenyl)-2-(2-chlorophenyl)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(3,4-methylenedioxyphenyl)-2-(2-chlorophenyl)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(3,5-difluoro-4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(3,5-dichloro-4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(difluoromethyl)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(methylthio)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(phenylthio)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-fluorophenyl)thio)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-chlorophenyl)thio)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-bromophenyl)thio)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-difluorophenyl)thio)thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(3,5-dichlorophenyl)thio]thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(4-fluorophenyl)thio]thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(4-chlorophenyl)thio]thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(4-bromophenyl)thio]thiazole;
5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-methylphenyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(benzylthio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-fluorobenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-chlorobenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-bromobenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-difluorobenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-fluorobenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-chlorobenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-bromobenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-methylbenzyl)thio)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(ethylsulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(methylsulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(phenylsulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-fluorophenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-chlorophenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-bromophenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-difluorophenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-dichlorophenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-fluorophenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-chlorophenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-bromophenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-methylphenyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(benzylsulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-fluorobenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-chlorobenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-bromobenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-difluorobenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-fluorobenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-chlorobenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-bromobenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-methylbenzyl)sulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(fluoromethylsulfonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(acetyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(trifluoroacetyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(benzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3-fluorobenzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3-chlorobenzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3-bromobenzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3,5-difluorobenzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3,5-dichlorobenzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-fluorobenzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-chlorobenzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-bromobenzoyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-methylbenzoyl)thiazole;

methyl [5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]carboxylate;

ethyl [5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]carboxylate;

propyl [5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]carboxylate;

butyl [5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]carboxylate;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(hydroxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(methoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(phenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3-fluorophenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3-chlorophenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3-bromophenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3,5-difluorophenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(3,5-dichlorophenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-fluorophenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-chlorophenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-bromophenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(4-methylphenoxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(benzyloxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(cyanomethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(2-quinolylmethyloxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(2-naphthylmethyloxymethyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(N-phenylaminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(3-fluorophenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(3-chlorophenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(3-bromophenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(3,5-difluorophenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(3,5-dichlorophenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(4-fluorophenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(4-chlorophenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(4-bromophenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-[(4-methylphenyl)aminocarbonyl]thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(benzylaminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-fluorobenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-chlorobenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-bromobenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-difluorobenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-fluorobenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-chlorobenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-bromobenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-methylbenzyl)aminocarbonyl)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(benzoylamino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-fluorobenzoyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-chlorobenzoyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3-bromobenzoyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-difluorobenzoyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((3,5-dichlorobenzoyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-fluorobenzoyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-chlorobenzoylamino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-bromobenzoyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-((4-methylbenzoyl)amino)thiazole;

5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-(phenylacetyl)aminothiazole;

2-((4-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-4-phenyl-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-4-(3-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

4-(2,4-difluorophenyl)-2-(2-chlorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-4-(2-methylphenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-5-[(4-methylsulfonyl)phenyl]-4-(2-thienyl)thiazole;

2-(2-chlorophenyl)-5-[(4-methylsulfonyl)phenyl]-4-(3-thienyl)thiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-(4-pyridyl)thiazole;

2-(2-chlorophenyl)-4-(2-chlorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-4-(4-methoxyphenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-((2-thienyl)sulfonylmethyl)-4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-((2-thienyl)sulfonylbromomethyl)-4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-5-[(4-methylsulfonyl)phenyl]-4-(4-methylphenyl)thiazole;

2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

ethyl [4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]carboxylate;

2-(cyanomethyl)-4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

[5-[(4-methylsulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]acetic acid;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-benzylthiazole;

2-(3-[4-bromophenyl]propyl)-4-(4-fluorophenyl))-5-[(4-methylsulfonyl)phenyl]thiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]thiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-trifluoromethylthiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-(2-thienyl)thiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-(5-bromo-2-thienyl)thiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-(3-pyridyl)thiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-methylthiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-benzylaminothiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-(1-piperidinyl)thiazole;

4-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-2-(1-propylamino)thiazole;

4-[4-(4-bromophenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-phenyl-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-chlorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(N-hexylamino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(N-methylamino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(N-ethylamino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(N-*tert*-butylamino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(N-(4-phenoxyphenyl)amino)-5-thiazolyl]benzenesulfonamide;

ethyl 4-[[5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]amino]benzoate;

ethyl 3-[[5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]amino]benzoate;

4-[4-(4-fluorophenyl)-2-(2-phenylethyl-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(N-(3,5-dichlorophenyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(N-butylamino)-5-thiazolyl]benzenesulfonamide;

4-[[5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]amino]benzoic acid;

3-[[5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]amino]benzoic acid;

4-[4-(4-fluorophenyl)-2-ethyl-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3-phenylpropyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-((3-chlorophenoxy)methyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-(2-methyl-4-thiazolyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(2-fluorophenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(2,5-difluorophenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-(2,3,4,5,6-pentafluorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-((2-chlorophenoxy)methyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(2-fluorophenyl)-2-((3-chlorophenoxy)methyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-((3,5-dichlorophenoxy)methyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(2-fluorophenyl)-2-((4-methoxyphenoxy)methyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-bromophenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-methylthiophenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(3-fluoro-4-methoxyphenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(3-chloro-4-methoxyphenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(3-chloro-4-methylphenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(3-methyl-4-chlorophenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(3,4-methylenedioxyphenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(3,5-difluoro-4-methoxyphenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(3,5-dichloro-4-methoxyphenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(difluoromethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(methylthio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(phenylthio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-fluorophenyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-chlorophenyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-bromophenyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-difluorophenyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-[(3,5-dichlorophenyl)thio]-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-[(4-fluorophenyl)thio]-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-[(4-chlorophenyl)thio]-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-[(4-bromophenyl)thio]-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-methylphenyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(benzylthio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-fluorobenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-chlorobenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-bromobenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-difluorobenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-fluorobenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-chlorobenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-bromobenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-methylbenzyl)thio)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(ethylsulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(methylsulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(phenylsulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-fluorophenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-chlorophenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-bromophenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-difluorophenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-dichlorophenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-fluorophenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-chlorophenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-bromophenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-methylphenyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(benzylsulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-fluorobenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-chlorobenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-bromobenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-difluorobenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-fluorobenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-chlorobenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-bromobenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-methylbenzyl)sulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(fluoromethylsulfonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(acetyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(trifluoroacetyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(benzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3-fluorobenzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3-chlorobenzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3-bromobenzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3,5-difluorobenzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3,5-dichlorobenzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-fluorobenzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-chlorobenzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-bromobenzoyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-methylbenzoyl)-5-thiazolyl]benzenesulfonamide;

methyl [5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]carboxylate;

ethyl [5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]carboxylate;

propyl [5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]carboxylate;

butyl [5-[(4-aminosulfonyl)phenyl]-4-(4-fluorophenyl)-2-thiazolyl]carboxylate;

4-[4-(4-fluorophenyl)-2-(hydroxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(methoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(phenoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3-fluorophenoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3-chlorophenoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3-bromophenoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3,5-difluorophenoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3,5-dichlorophenoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-fluorophenoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-chlorophenoxymethyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-bromophenoxymethyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-(4-methylphenoxymethyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-(benzyloxymethyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-(cyanomethyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-(2-quinolylmethyloxymethyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-(2-naphthylmethyloxymethyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-(N-phenylaminocarbonyl)-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-[(3-fluorophenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-[(3-chlorophenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-[(3-bromophenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-[(3,5-difluorophenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-[(3,5-dichlorophenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-[(4-fluorophenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-[(4-chlorophenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-2-[(4-bromophenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-[(4-methylphenyl)aminocarbonyl]-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(benzylaminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-fluorobenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-chlorobenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-bromobenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-difluorobenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-fluorobenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-chlorobenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-bromobenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-methylbenzyl)aminocarbonyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(benzoylamino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-fluorobenzoyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-chlorobenzoyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3-bromobenzoyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-difluorobenzoyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-dichlorobenzoyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-fluorobenzoyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-chlorobenzoylamino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-bromobenzoyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((4-methylbenzoyl)amino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(phenylacetyl)amino-5-thiazolyl]benzenesulfonamide;

4-[2-((4-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-phenyl-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-(3-fluorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(2,4-difluorophenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-(2-methylphenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-(2-thienyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-(3-thienyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(4-pyridyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-(4-methoxyphenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-((2-thienyl)sulfonylmethyl)-4-(4-fluorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-((2-thienyl)sulfonylbromomethyl)-4-(4-fluorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(2-chlorophenyl)-4-(4-methylphenyl)-5-thiazolyl]benzenesulfonamide;

ethyl [4-(4-fluorophenyl)-5-[(4-aminosulfonyl)phenyl]-2-thiazolyl]carboxylate;

4-[2-(cyanomethyl)-4-(4-fluorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[2-(*tert*-butyl)-4-(4-fluorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-benzyl-5-thiazolyl]benzenesulfonamide;

4-[2-(3-[4-bromophenyl]propyl)-4-(4-fluorophenyl))-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-trifluoromethyl-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(2-thienyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(5-bromo-2-thienyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(3-pyridyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-methyl-5-thiazolyl]benzenesulfonamide;

4-[4-(4-chlorophenyl)-2-methyl-5-thiazolyl]benzenesulfonamide;

4-[4-(3-fluoro-4-methoxyphenyl)-2-methyl-5-thiazolyl]benzenesulfonamide;

4-[4-phenyl-2-methyl-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-benzylamino-5-thiazolyl]benzenesulfonamide;

4-[4-(3-fluoro-4-methoxyphenyl)-2-benzylamino-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(1-piperidinyl)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(1-propylamino)-5-thiazolyl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-(2-chlorophenyl)thiazol-5-yl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-2-((3,5-dichlorophenoxy)methyl)-5-thiazolyl]benzenesulfonamide;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(trifluoromethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-chlorophenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-methylphenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-bromophenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-methylthiophenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(3-fluoro-4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(3-chloro-4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(3-chloro-4-methylphenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(3-methyl-4-chlorophenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(3,4-methylenedioxyphenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(3,5-difluoro-4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(3,5-dichloro-4-methoxyphenyl)-2-(2-chlorophenyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-methylthiazole;
4-[(4-methylsulfonyl)phenyl]-5-(3-fluoro-4-methoxyphenyl)-2-(2-methyl-4-thiazolyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(difluoromethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(methylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-fluoro-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-chloro-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-bromo-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-difluoro-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-dichloro-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-fluoro-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-chloro-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-bromo-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-methyl-phenylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(benzylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-fluorobenzylthio)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-chlorobenzylthio)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-bromobenzylthio)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-difluorobenzylthio)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-dichlorobenzylthio)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-fluorobenzylthio)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-chlorobenzylthio)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-bromobenzylthio)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-methylbenzylthio)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(ethylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(methylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(phenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-fluorophenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-chlorophenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-bromophenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-difluorophenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-dichlorophenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-fluorophenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-chlorophenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-bromophenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-methylphenylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(benzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-fluorobenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-chlorobenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-bromobenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-difluorobenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-dichlorobenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-fluorobenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-chlorobenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-bromobenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-methylbenzylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(fluoromethylsulfonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(acetyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(trifluoroacetyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(benzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-fluorobenzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-chlorobenzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-bromobenzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-difluorobenzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-dichlorobenzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-fluorobenzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-chlorobenzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-bromobenzoyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-methylbenzoyl)thiazole;

[4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-thiazolyl]acetic acid;

[4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-thiazolyl]propanoic acid;

[4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-thiazolyl]butanoic acid;

[4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-thiazolyl]pentanoic acid;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(hydroxymethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(methoxymethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(phenyloxymethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-fluorophenyloxymethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-chlorophenyloxymethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-bromophenyloxymethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-difluorophenyloxymethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-dichlorophenyloxymethyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-fluorophenyloxymethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-chlorophenyloxymethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-bromophenyloxymethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-methylphenyloxymethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(benzyloxymethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(cyanomethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(2-quinolylmethyloxymethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(2-naphthylmethyloxymethyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(N-phenylaminocarbonyl)thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3-fluorophenyl)aminocarbonyl]thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3-chlorophenyl)aminocarbonyl]thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3-bromophenyl)aminocarbonyl]thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3,5-difluorophenyl)aminocarbonyl]thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3,5-dichlorophenyl)aminocarbonyl]thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(4-fluorophenyl)aminocarbonyl]thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(4-chlorophenyl)aminocarbonyl]thiazole;
4-(4-methylsulfonyl)-5-(4-fluorophenyl)-2-[(4-bromophenyl)aminocarbonyl]thiazole;
4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(4-methylphenyl)aminocarbonyl]thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(benzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-fluorobenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-chlorobenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-bromobenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-difluorobenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-dichlorobenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-fluorobenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-chlorobenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-bromobenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-methylbenzylaminocarbonyl)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(benzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-fluorobenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-chlorobenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3-bromobenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-difluorobenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(3,5-dichlorobenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-fluorobenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-chlorobenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-bromobenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(4-methylbenzoylamino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(phenylacetyl)aminothiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3-fluorophenyl)acetyl]aminothiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3-chlorophenyl)acetyl]aminothiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3-bromophenyl)acetyl]amino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3,5-difluorophenyl)acetyl]amino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(3,5-dichlorophenyl)acetyl]amino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(4-fluorophenyl)acetyl]amino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(4-chlorophenyl)acetyl]amino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(4-bromophenyl)acetyl]amino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-[(4-methylphenyl)acetyl]amino)thiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(fluoromethylsulfonyl)aminothiazole;

4-[(4-methylsulfonyl)phenyl]-5-(4-fluorophenyl)-2-(methylsulfonyl)aminothiazole;

4-[5-(4-chlorophenyl)-2-methyl-4-thiazolyl]benzenesulfonamide;

4-[5-(4-bromophenyl)-2-methyl-4-thiazolyl]benzenesulfonamide;

4-[2-methyl-5-phenyl-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(trifluoromethyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-bromophenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-methylthiophenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(3-chloro-4-methoxyphenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(3-chloro-4-methylphenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(3-methyl-4-chlorophenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(3,4-methylenedioxyphenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(3,5-difluoro-4-methoxyphenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(3,5-dichloro-4-methoxyphenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-methoxyphenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-methylphenyl)-2-(2-chlorophenyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(difluoromethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(methylthio)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(phenylthio)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-((3-fluorophenyl)thio)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-((3-chlorophenyl)thio)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-((3-bromophenyl)thio)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-((3,5-difluorophenyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(3,5-dichlorophenyl)thio]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(4-fluorophenyl)thio]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(4-chlorophenyl)thio]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(4-bromophenyl)thio]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-methylphenyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(benzylthio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-fluorobenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-chlorobenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-bromobenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-difluorobenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-fluorobenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-chlorobenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-bromobenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-methylbenzyl)thio)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(ethylsulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(methylsulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(phenylsulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-fluorophenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-chlorophenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-bromophenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-difluorophenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-dichlorophenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-fluorophenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-chlorophenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-bromophenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-methylphenyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(benzylsulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-fluorobenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-chlorobenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-bromobenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-difluorobenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-fluorobenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-chlorobenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-bromobenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-methylbenzyl)sulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(fluoromethylsulfonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(acetyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(trifluoroacetyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(benzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(3-fluorobenzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(3-chlorobenzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(3-bromobenzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(3,5-difluorobenzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(3,5-dichlorobenzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(4-fluorobenzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(4-chlorobenzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(4-bromobenzoyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(4-methylbenzoyl)-4-thiazolyl]benzenesulfonamide;

methyl [4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)-2-thiazolyl]carboxylate;

ethyl [4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)-2-thiazolyl]carboxylate;

propyl [4-[(4-aminosulfonyl)phenyl)-5-(4-fluorophenyl)-2-thiazolyl]carboxylate;

butyl [4-[(4-aminosulfonyl)phenyl]-5-(4-fluorophenyl)-2-thiazolyl]carboxylate;

4-[5-(4-fluorophenyl)-2-(hydroxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(methoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(phenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(3-fluorophenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(3-chlorophenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(3-bromophenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(3,5-difluorophenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(3,5-dichlorophenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(4-fluorophenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(4-chlorophenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(4-bromophenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(4-methylphenoxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(benzyloxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(cyanomethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(2-quinolylmethyloxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(2-naphthylmethyloxymethyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(N-phenylaminocarbonyl)-4-thiazolyl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-[(3-fluorophenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(3-chlorophenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(3-bromophenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(3,5-difluorophenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(3,5-dichlorophenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(4-fluorophenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(4-chlorophenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(4-bromophenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-[(4-methylphenyl)aminocarbonyl]-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(benzylaminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-fluorobenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-chlorobenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-bromobenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-difluorobenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-dichlorobenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-fluorobenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-chlorobenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-bromobenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-methylbenzyl)aminocarbonyl)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(benzoylamino)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-fluorobenzoyl)amino)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-chlorobenzoyl)amino)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3-bromobenzoyl)amino)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-difluorobenzoyl)amino)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((3,5-dichlorobenzoyl)amino)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-fluorobenzoyl)amino)-4-thiazolyl]benzenesulfonamide;

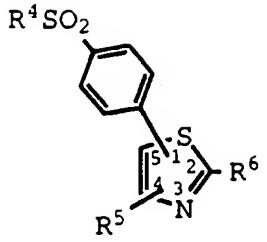
4-[5-(4-fluorophenyl)-2-((4-chlorobenzoylamino)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-bromobenzoyl)amino)-4-thiazolyl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-((4-methylbenzoyl)amino)-4-thiazolyl]benzenesulfonamide; and

4-[5-(4-fluorophenyl)-2-(phenylacetyl)amino-4-thiazolyl]benzenesulfonamide.

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



II

wherein R^4 is selected from alkyl and amino;

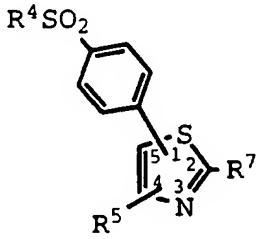
wherein R^5 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aminosulfonyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, heterocyclic and nitro; and

wherein R^6 is selected from halo, amino, alkoxy, nitro, hydroxyl, aminocarbonyl, acyl, alkylaminocarbonyl, arylaminocarbonyl, alkenyl, alkynyl, haloalkoxy, alkylamino, arylamino, aralkylamino, alkoxycarbonylalkyl, alkylaminoalkyl, heterocycloalkyl, aralkyl, cyanoalkyl, N-alkylsulfonylamino, heteroarylsulfonylalkyl, heteroarylsulfonylhaloalkyl, aryloxyalkyl, aralkyloxyalkyl, aryl and heterocyclo, wherein the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, haloalkyl, haloalkoxy, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, amino, acyl and alkylamino; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula II wherein R^4 is selected from lower alkyl and amino; wherein R^5 is selected from aryl, lower cycloalkyl, lower cycloalkenyl and heteroaryl; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower haloalkylsulfonyl, aminosulfonyl, lower alkyl, lower alkenyl, lower alkynyl, cyano, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, acyl, lower N-alkylaminocarbonyl, lower N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, heterocyclic and nitro; and wherein R^6 is selected from halo, amino, lower alkoxy, nitro, hydroxyl, aminocarbonyl, acyl, lower alkylaminocarbonyl, lower arylaminocarbonyl, lower alkenyl, lower alkynyl, lower haloalkoxy, lower alkylamino, phenylamino, lower aralkylamino, lower alkoxycarbonylalkyl, lower alkylaminoalkyl, lower heterocycloalkyl, lower aralkyl, lower cyanoalkyl, lower N-alkylsulfonylamino, lower heteroarylsulfonylalkyl, lower heteroarylsulfonylhaloalkyl, lower aryloxyalkyl, lower aralkyloxyalkyl, phenyl optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino, and heterocyclic optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy,

lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a second subclass of compounds of high interest represented by Formula III:



III

wherein R^4 is selected from alkyl and amino;

wherein R^5 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aminosulfonyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, heterocyclic and nitro; and

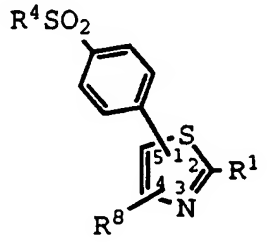
wherein R^7 is selected from hydrido, alkyl, haloalkyl, cyano, hydroxyalkyl, alkoxyalkyl, carboxyl, carboxyalkyl, and alkoxycarbonyl;

provided that R^5 is not 4-fluorophenyl when R^7 is methyl; further provided R^5 is not phenyl substituted with α,α-bis(methyl)methanol; and further provided that R^4 is not methyl when R^7 is α,α-bis(trifluoromethyl)methanol; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula III wherein R^4 is selected from

lower alkyl and amino; wherein R^5 is selected from aryl, lower cycloalkyl, lower cycloalkenyl and heteroaryl; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower haloalkylsulfonyl, aminosulfonyl, lower alkyl, lower alkenyl, lower alkynyl, cyano, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, acyl, lower N-alkylaminocarbonyl, lower N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, heterocyclic and nitro; and wherein R^7 is selected from hydrido, lower alkyl, lower haloalkyl, cyano, lower hydroxyalkyl, lower alkoxyalkyl, carboxyl, lower carboxyalkyl, and lower alkoxycarbonyl; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a third subclass of compounds of high interest represented by Formula IV:



IV

wherein R^1 is selected from hydrido, halo, amino, alkoxy, cyano, nitro, hydroxyl, aminocarbonyl, acyl, alkylaminocarbonyl, arylaminocarbonyl, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, carboxyl, carboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylaminoalkyl, heterocycloalkyl, aralkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, N-alkylsulfonylamino,

heteroarylsulfonylalkyl, heteroarylsulfonylhaloalkyl, aryloxyalkyl, aralkyloxyalkyl, aryl and heterocyclo, wherein the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, haloalkyl, haloalkoxy, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, amino, acyl and alkylamino;

wherein R^4 is selected from alkyl and amino; and

wherein R^8 is heterocyclic; wherein R^8 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, and nitro;

or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula IV wherein R^1 is selected from hydrido, halo, amino, lower alkoxy, cyano, nitro, hydroxyl, aminocarbonyl, acyl, lower alkylaminocarbonyl, phenylaminocarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, phenylamino, lower aralkylamino, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminoalkyl, lower heterocycloalkyl, lower aralkyl, lower hydroxyalkyl, lower alkoxyalkyl, lower cyanoalkyl, lower N-alkylsulfonylamino, lower heteroarylsulfonylalkyl, lower heteroarylsulfonylhaloalkyl, lower aryloxyalkyl, aralkyloxyalkyl, aryl optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower

alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino, and heterocyclic optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino; wherein R^4 is selected from lower alkyl and amino; and wherein R^8 is nitrogen-containing heteroaryl optionally substituted at a substitutable position with one or more substituents independently selected from halo, alkyl, alkoxy, alkylthio, amino and alkylamino; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula IV wherein R^1 is selected from hydrido, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyanomethyl, cyanoethyl, cyanopropyl, methylamino, ethylamino, propylamino, butylamino, *tert*-butylamino, pentylamino, hexylamino, phenethyl, phenylpropyl, benzyl, phenylamino, thienylsulfonylmethyl, thienylsulfonylbromomethyl, benzylamino, phenoxymethyl, 3,5-dichlorophenylamino, 3,5-dichlorophenoxymethyl, 3-chlorophenoxymethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, phenyl optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo,

methoxy, ethoxy, propoxy, butoxy, isopropoxy and *tert*-butoxy, and a heterocyclic radical selected from thienyl, pyridyl, furyl, oxazolyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolinyl, imidazolyl, thiazolyl, pyrrolyl, pyrazolyl and triazolyl, optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl and *tert*-butyl; wherein R^4 is methyl or amino; and wherein R^8 is selected from pyridyl, thienyl, thiazolyl, oxazolyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolinyl, imidazolyl, and benzimidazolyl, wherein R^8 is optionally substituted at a substitutable position with one or more substituents independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, propoxy, butoxy, isobutoxy, pentoxy, methylthio, amino, N-methylamino and N,N-dimethylamino; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula IV consists of compounds and pharmaceutically-acceptable salts thereof as follows:

2-(2-chlorophenyl)-4-(4-pyridyl)-5-(4-methylsulfonylphenyl)thiazole;

2-(3-chloro-4-fluorophenyl)-4-(4-pyridyl)-5-(4-methylsulfonylphenyl)thiazole;

5-(4-pyridyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

2-[(3,5-dichlorophenoxy)methyl)-4-(4-pyridyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-4-(4-pyrazinyl)-5-(4-methylsulfonylphenyl)thiazole;

2-((3-chlorophenoxy)methyl)-4-(4-pyridyl)-5-(4-methylsulfonylphenyl)thiazole;

4-(4-pyridyl)-5-[4-(methylsulfonyl)phenyl]-2-(2-methyl-4-thiazolyl)thiazole;

4-(4-pyridyl)-2-[(4-methoxyphenoxy)methyl]-5-[4-(methylsulfonyl)phenyl]thiazole;

4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-2-phenylthiazole;

4-(4-pyridyl)-2-n-hexylamino-5-(4-methylsulfonylphenyl)thiazole;

2-butylamino-4-(4-pyridyl)-5-(4-methylsulfonylphenyl)thiazole;

4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-2-methylaminothiazole;

4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-2-(4-methoxyphenyl)thiazole;

2-ethylamino-4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-thiazole;

2-*tert*-butylamino-4-(4-pyridyl)-5-(4-methylsulfonylphenyl)thiazole;

2-(3,5-dichlorophenylamino)-4-(4-pyridyl)-5-(4-methylsulfonylphenyl)thiazole;

5-(4-pyridyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole; and

4-(4-pyridyl)-5-(4-methylsulfonylphenyl)-2-(2,3,4,5,6-pentafluorophenyl)thiazole.

Compounds of Formula IV would also be capable of inhibiting cytokines, such as TNF, IL-1, IL-6, and IL-8. As such, the compounds can be used in the manufacture of a medicament or in a method for the treatment for the prophylactic or therapeutic treatment of diseases

mediated by cytokines, such as TNF, IL-1, IL-6, and IL-8.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, iso-amyl, hexyl and the like. Where the term "alkenyl" is used, it embraces linear or branched carbon carbon double bond-containing radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Suitable "lower alkenyl" may be a straight or branched one such as vinyl, allyl, isopropenyl, propenyl, butenyl, pentenyl or the like, in which preferably one is isopropenyl. Said lower alkenyl may be substituted with cyano. Where the term "alkynyl" is used, it embraces linear or branched carbon carbon triple bond-containing radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Suitable "lower alkynyl" may be a straight or branched radical such as ethynyl, propynyl, propargyl or the like, in which preferably one is propargyl. The term "halo" means halogens such

as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include

methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or haloalkoxyalkyl radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces unsaturated cyclic radicals having three to ten carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having about five to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Such aryl radicals may be substituted at a substitutable position with one or more substituents selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy. The terms "heterocyclic" and "heterocyclo" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals

include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g.

benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may be substituted at a substitutable position with one or more substituents selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy. More preferred heteroaryl radicals include five to six membered heteroaryl radicals. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocycloalkyl radicals are "lower heterocycloalkyl" radicals having one to six carbon atoms and a heterocyclic radical. Examples include such radicals as pyrrolidinylmethyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl

and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkylsulfonyl" radicals. More preferred haloalkylsulfonyl radicals are "lower haloalkylsulfonyl" radicals having one or more halo atoms attached to lower alkylsulfonyl radicals as described above. Examples of such lower haloalkylsulfonyl radicals include fluoromethylsulfonyl, trifluoromethylsulfonyl and chloromethylsulfonyl. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denotes NH_2O_2S-. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes $-(C=O)-$. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkyl" embraces radicals having

"alkoxycarbonyl", as defined above substituted to an alkyl radical. The term "carboxyalkyl" embraces carboxylic acids attached to an alkyl radical so as to have a free acid remaining. The alkanoyl radicals may be a substituted or unsubstituted one such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl or the like, in which the preferable one is formyl, acetyl, propionyl or trifluoroacetyl. The "aroyl" radicals may be benzoyl, naphthoyl, toluoyl, di(*tert*-butyl)benzoyl and the like and the aryl in said aroyl may be additionally substituted. The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may be substituted at a substitutable position with one or more substituents selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "aryloxy" embrace oxy-containing aryl radicals attached through an oxygen atom to other radicals. More preferred aryloxy radicals are "lower aryloxy" radicals having a phenyl radical. An example of such radicals is phenoxy. The term "aryloxyalkyl" embraces alkyl radicals having one or more aryloxy radicals attached to the alkyl radical, that is, to form monoaryloxyalkyl and diaryloxyalkyl radicals. The "aryloxy" or "aryloxyalkyl" radicals may be further substituted at a substitutable position with one or more alkyl, alkoxy or halo radicals. to provide haloaryloxyalkyl radicals alkylaryloxy radicals, and the like. Examples of such radicals include chlorophenoxy and methylphenoxy. The term "aralkyloxy" embrace oxy-containing aralkyl

radicals attached through an oxygen atom to other radicals. The term "aralkyloxyalkyl" embraces alkyl radicals having one or more aralkyloxy radicals attached to the alkyl radical, that is, to form monoaralkyloxyalkyl and diaralkyloxyalkyl radicals. The "aralkyloxy" or "aralkyloxyalkyl" radicals may be further substituted on the aryl ring portion of the radical. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl, aminoethyl and aminobutyl. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with at least one alkyl radical. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having one to six carbon atoms attached to a lower aminoalkyl radical as described above. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. Arylamino radicals may be substituted at a substitutable position with one or more alkyl, cyano, alkoxy, alkoxycarbonyl or halo radicals. The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals, such as N-benzylamino, N-phenethylamino and phenpropylamino. The "aralkylamino" or "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aminocarbonyl", whether used by itself or with other terms such as "N-

alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl", denotes a radical formed by an amino substituted carbonyl, or $-C(=O)NH_2$. The term "alkylaminocarbonyl" embraces "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl", which denotes aminocarbonyl groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The N-alkylaminocarbonyl may be substituted with halo or an unsubstituted one such as N-methylaminocarbonyl, N-ethylaminocarbonyl, N-propylaminocarbonyl, N,N-dimethylaminocarbonyl, 2,2,2-trifluoroethylaminocarbonyl or the like. The terms "N-monoarylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The N-arylaminocarbonyl may be phenylaminocarbonyl, naphthylaminocarbonyl, tolylaminocarbonyl, xylylaminocarbonyl, mesitylaminocarbonyl, cumenylaminocarbonyl, and the like, in which the preferable one is phenylaminocarbonyl. The term "alkylsulfonylamino" embraces radicals having an alkylsulfonyl radical attached to a nitrogen atom. More preferred are "lower alkylsulfonylamino" having alkylsulfonyl radicals of one to six carbon atoms attached to the nitrogen. The terms "heteroarylsulfonylalkyl" and "heteroarylsulfonylhaloalkyl" denotes heteroaryl radicals attached through a sulfonyl bridging group to an alkyl radical or haloalkyl radical, respectively. More preferred heteroarylsulfonylalkyl and heteroarylsulfonylhaloalkyl radicals are "lower heteroarylsulfonylalkyl" and "lower heteroarylsulfonylhaloalkyl" radicals where the alkyl and haloalkyl portions have 1 to 6 carbon atoms. Examples of such radicals include thienylsulfonylmethyl, and thienylsulfonylbromomethyl.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having or susceptible to such inflammation or disorder, a therapeutically-effective amount of a compound of Formula I.

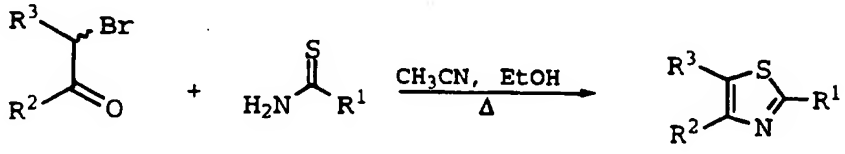
Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, *p*-hydroxybenzoic,

phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-X, wherein the R^1-R^8 substituents are as defined for Formulas I-IV, above, except where further noted.

SCHEME I

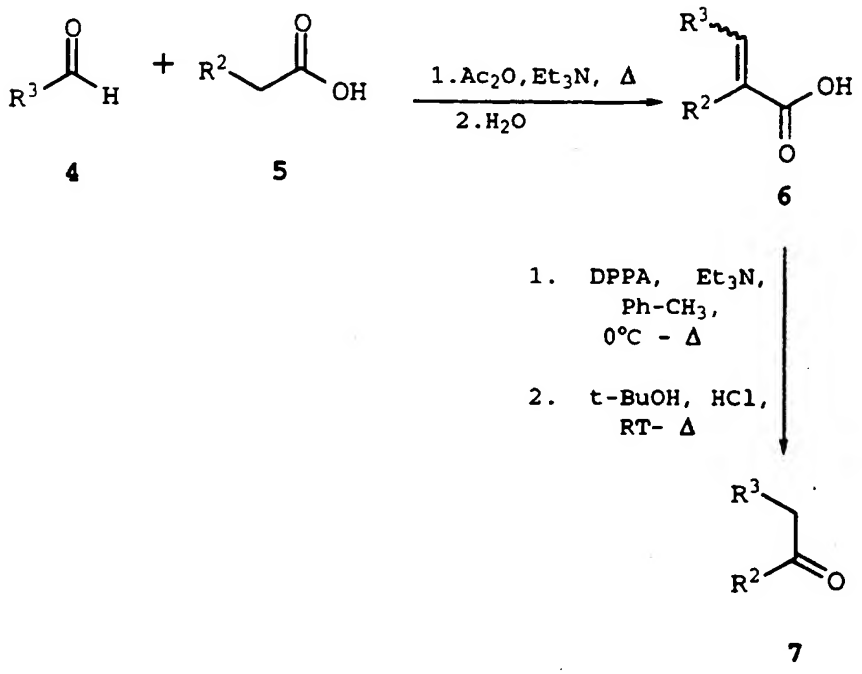


1 2 3

Synthetic Scheme I shows the procedure used to prepare the antiinflammatory substituted thiazoles **3** of the present invention from α-haloketones **1**. The α-haloketones **1**, such as 2-bromo-ethanone, are reacted with a thioamide **2** or thiourea in acetonitrile and an alcohol, such as methanol and ethanol, to give the 4,5-

substituted thiazoles **3** via the Hantzsch synthesis (R. Wiley et al, The Preparation of Thiazoles, **ORGANIC REACTIONS**, VOLUME 6, (1951)).

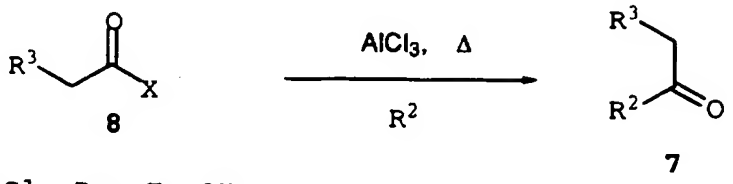
SCHEME II



Synthetic Scheme II shows the four step procedure which can be used to prepare the substituted ketone compounds **7** from aldehyde **4** and acid **5**. In step one, aldehyde **4** and substituted acetic acid **5** are heated in acetic anhydride and triethylamine to form the 2,3-disubstituted acrylic acids **6** via a Perkin condensation. In step two, the addition of water produces the corresponding 2,3-disubstituted acrylic acids **6**. In step three, the acrylic acids **6** are reacted with diphenylphosphorylazide (DPPA) and triethylamine in toluene at 0°C and then at room temperature to form acylazides. In step four, the crude acylazides are heated to form an isocyanate via a Curtius rearrangement. The isocyanate is trapped as the N-*tert*-butyloxycarbonyl enamine derivative via the addition of *tert*-butanol. Acidic hydrolysis using

concentrated HCl provides the substituted ketone **7** intermediates.

SCHEME III

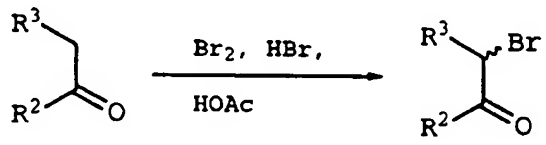


X=Cl, Br, F, OH

Synthetic Scheme III shows an alternative approach which can be used to prepare the substituted ketone intermediates **7** via the use of Friedel Crafts acylation. An acylating agent **8**, such as an acid chloride is treated with aluminum chloride in an inert solvent, such as methylene chloride, chloroform, nitrobenzene, dichlorobenzene or chlorobenzene, and reacted with R^2 to form ketone **7**.

Other synthetic approaches are possible to form the desired ketones. These alternatives include reacting appropriate Grignard or lithium reagents with substituted acetic acids or corresponding esters.

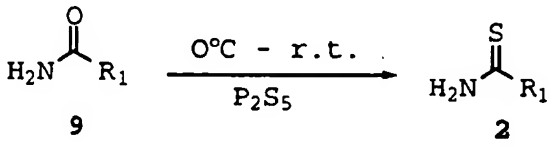
SCHEME IV



Synthetic Scheme IV shows the procedure which can be used to prepare the substituted haloketone compounds **1**. 1,2-Disubstituted ketone intermediates **7** from Synthetic Schemes II or II are readily brominated via the addition of bromine in acetic acid to form the 2-bromo-1,2-disubstituted ethanone intermediates **1**.

Alternative means of forming 2-haloketones **1** include the conversion of benzoins such as substituted 2-hydroxyethanones via use of reagents such as thionyl chloride, sulfuryl chloride, methylsulfonyl chloride/lithium chloride, triphenylphosphine dichloride or triphenylphosphine dibromide, among others. The conversion of simple desoxybenzions to the haloketones **1** is readily accomplished via use of halogenating reagents such as bromine, N-bromosuccinimide, N-chlorosuccinimide.

SCHEME V

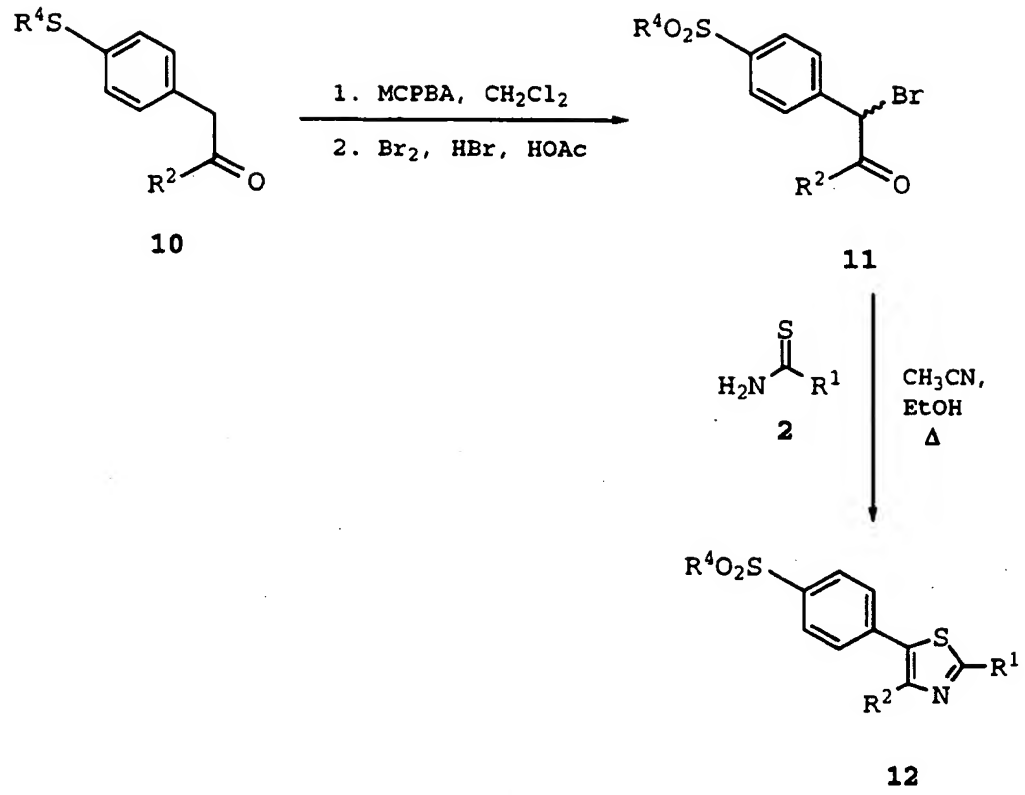


9 **2**

Synthetic Scheme V shows a procedure for the preparation of thioamides **2** by the thiation of the oxygen carboxamide **9** counterparts. The carboxamide **9** is dissolved in a solvent, such as diethyl ether, and cooled to about 0°C. The thiation reagent, such as phosphorous pentasulfide (P_2S_5 or P_4S_{10}) is added and maintained at a temperature below room temperature. The reaction is warmed to room temperature and stirred. The ethereal solution of the thioamide **2** can be decanted from the reaction mixture and used "as is".

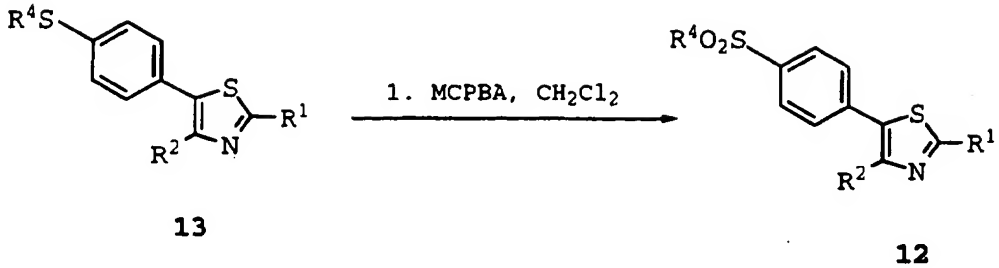
Alternative means of forming the thioamides **2** includes the use of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's Reagent) as the thiation reagent. The reaction is heated at reflux. In addition, thioamides **2** can be formed by the reaction of a suitable nitrile with hydrogen sulfide.

SCHEME VI



Synthetic Scheme VI shows a three step procedure which can be used to prepare alkylsulfonyl substituted thiazoles **12** from alkylthio substituted ketones **10**. In step one, the alkylthioether of ethanone **10**, where the thioether radical is located at R^3 and R^4 is an alkyl radical, is first oxidized to an alkylsulfone using *meta*-chloroperoxybenzoic acid (MCPBA) (2 eq) in methylene chloride at 0°C and warmed to room temperature. In step two, the alkylsulfonylketone, where the alkylsulfone radical is located at R^3, is brominated alpha to the carbonyl using bromine in HBr/HOAc to form the alkylsulfonyl-2-bromoethanone **11**. Condensation of **11** with an appropriate thioamide or thiourea **2** provides the corresponding substituted 5-(4-alkylsulfonylphenyl)thiazole **12**. Alternatively, the procedure can be utilized to produce thiazoles having an alkylsulfonyl radical at R^2.

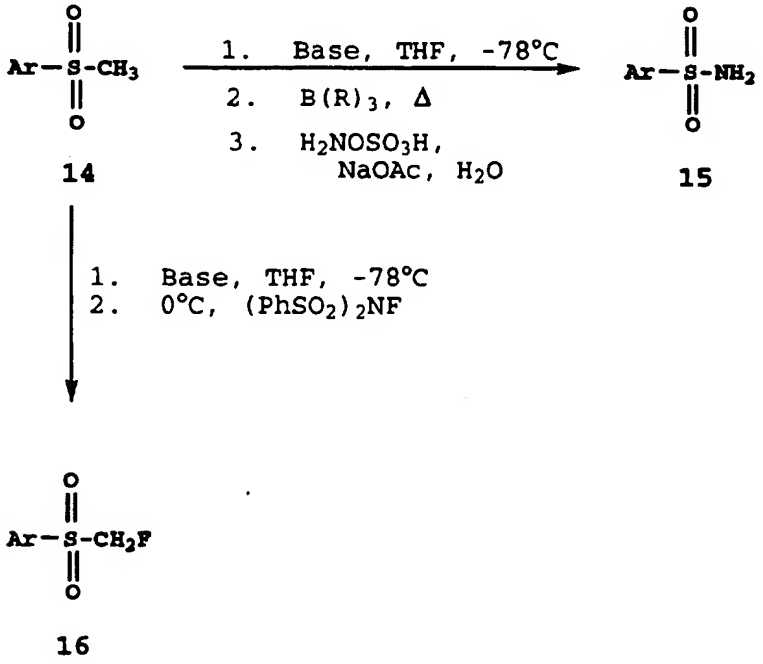
SCHEME VII



13 12

An alternative synthesis of the alkylsulfonyl substituted thiazoles **12** is accomplished as shown in Synthetic Scheme VII. Thiazole **13**, having an alkylthiophenyl radical at R^3 where R^4 is an alkyl radical, is oxidized with MCPBA (2 equivalents) in methylene chloride to form the alkylsulfone **12**. Other suitable oxidizing agents include Oxone®, hydrogen peroxide, periodate, peracetic acid and the like. Alternatively, the procedure can be utilized to produce thiazoles having an alkylsulfonylphenyl radical at R^2.

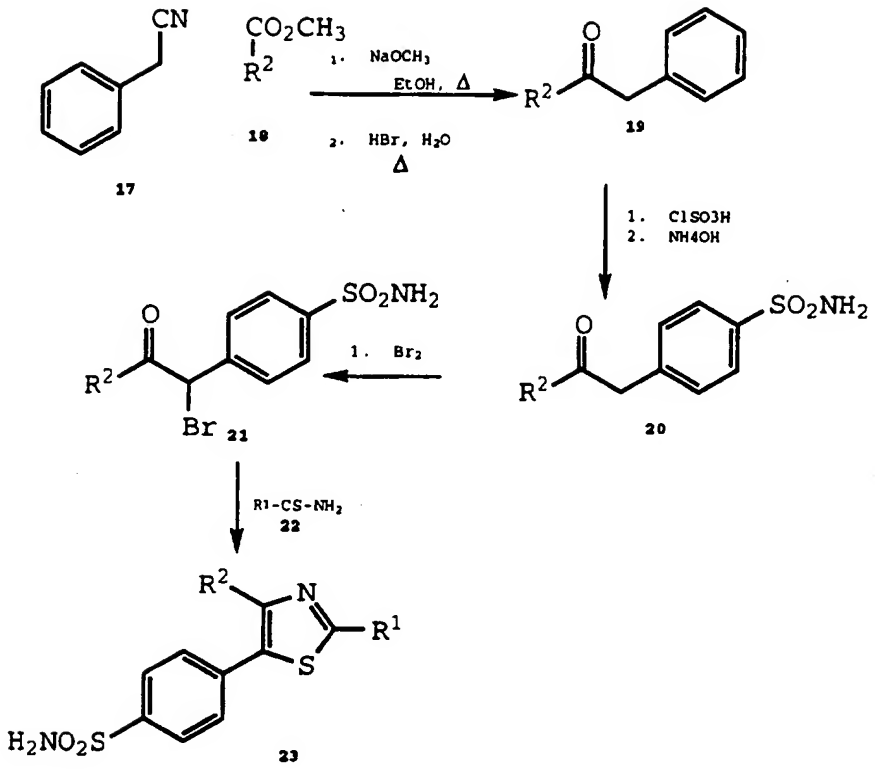
Scheme VIII



14 15 16

Synthetic Scheme VIII shows the three step procedure used to prepare sulfonamide antiinflammatory agents **15** and the two step procedure used to prepare fluoromethyl sulfone antiinflammatory agents **16** from their corresponding methyl sulfones **14**. In step one, a THF solution of the methyl sulfones **14** at -78°C is treated with an alkyllithium or organomagnesium (Grignard) reagent (RMgX), e.g., methyllithium, n-butyllithium, etc. In step two, the anions generated in step one are treated with an organoborane, e.g., triethylborane, tributylborane, etc., at -78°C then warmed to ambient temperature prior to stirring at reflux. An alternative to the boron chemistry involves room temperature alkylation, such as with trimethylsilylmethylhalides, followed by treatment with tetrabutylammonium fluoride (1M in THF). In step three, an aqueous solution of sodium acetate and hydroxyamine-O-sulfonic acid is added to provide the corresponding sulfonamide antiinflammatory agents **15** of this invention. Alternatively, the anion solutions generated in step one may be warmed to 0°C and treated with N-fluorodibenzenesulfonamide to provide the corresponding fluoromethyl sulfone antiinflammatory agents **16** of this invention.

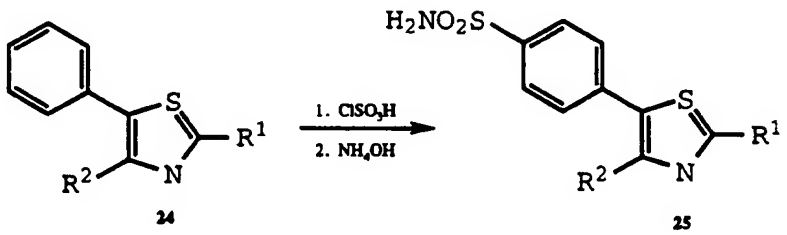
Scheme IX



Synthetic Scheme IX shows the four step procedure used to prepare sulfonamide antiinflammatory agents **23** of the present invention. Synthesis of deoxybenzoin intermediates can be accomplished via condensation of an appropriate "benzylate" anion with an appropriate ester. As shown in Scheme IX, phenylacetonitrile **17** upon deprotonation with an appropriate base (eg. sodium methoxide, sodium hydride, lithium diisopropyl amide, etc.), will react with an appropriate ester **18** to form an α-cyanoketone. Acid catalyzed hydrolysis of the nitrile and subsequent decarboxylation yield the ketone intermediate **19**. Chlorosulfonation of the ketone **19**) will yield a sulfonyl chloride intermediate which reacts readily with ammonia (eg. NH_4OH) to yield the p-benzenesulfonamide derivative **20**. Bromination of this ketone **20** with Br_2 using HBr as catalyst yields the corresponding alpha-bromoketone **21**. This bromoketone

can be condensed with thioamides and thioureas **22** in the Hantzsch reaction to form the thiazole nucleus **23**.

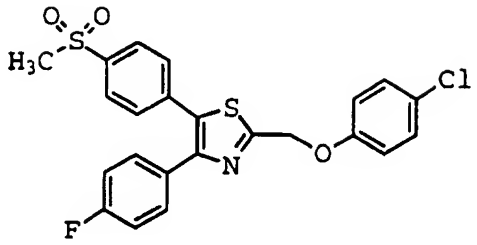
Scheme X



Alternatively, the sulfonamide moiety can be introduced after the thiazole ring has already been formed. Treatment of an appropriately substituted phenyl-thiazole **24** with neat chlorosulfonic acid followed by reaction with ammonia yields the corresponding (5-thiazolyl)benezenesulfonamide **25**. The other regioisomer, (4-thiazolyl)benezenesulfonamide, can be prepared depending on the R^3 substituent. For example, if the phenyl radical at position 5 is substituted at the para position.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I-IV. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

Example 1



2-((4-Chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1 Preparation of 2-(4-fluorophenyl)-3-(4-methylthiophenyl)propenoic acid:

Acetic anhydride (500 mL), 4-(methylthio)benzaldehyde (100.2 g, 0.66 mol), 4-fluorophenylacetic acid (101.6 g, 0.66 mol), and triethylamine (68.1 g, 0.67 mol) were heated to reflux for 1.75 hours. The reaction was cooled to 110°C, and water (500 mL) was added cautiously. This caused the solution to reflux vigorously and the temperature to rise to 135°C. A yellow precipitate formed, and after cooling to room temperature, was collected by filtration, washed with water, and recrystallized from ethyl acetate/isooctane to provide the diarylpropenoic acid as yellow needles (135.2 g, 71%): mp 172-176°C. ^{1}H NMR (acetone-d_6) δ300 MHz 7.84 (s, 1H), 7.03-7.28 (m, 10H), 2.46 (s, 3H); ^{19}F NMR (acetone-d_6) -116.11 (m). Mass spectrum: M$^+$ 288.

Step 2: Preparation of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone:

The diarylpropenoic acid from Step 1 (226.5 g, 0.78 mol) was added to anhydrous toluene (800 mL) and triethylamine (81.2 g, 0.80 mol). After cooling to 0°C, diphenylphosphoryl azide (217.4 g, 0.79 mol) was added. The solution was stirred at 0°C for twenty minutes and at room temperature for 2.5 hours. The reaction was poured into water, extracted with ether,

dried over magnesium sulfate, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to reflux and a vigorous evolution of gas occurred. After 1.25 hours, *tert*-butyl alcohol (80 mL, 0.84 mol) was added to the reaction. After an additional twenty minutes, concentrated hydrochloric acid (41 mL) was added slowly causing the reaction to foam. The reaction was heated at 90°C overnight (14 hours) and after cooling, a white precipitate formed. The precipitate was isolated by filtration, washed with cold ether, and air dried to yield the desired ketone (182.7 g, 89%): mp 134.5-138°C. ^{1}H NMR (acetone-d_6) 300 MHz 8.16 (m, 2H), 7.24 (m, 6H), 4.34 (s, 2H), 2.46 (s, 3H); ^{19}F NMR (acetone-d_6) -107.88 (m).

Step 3: Preparation of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromoethanone:

The ketone from Step 2 (55.5 g, 0.21 mol) was added to acetic acid (250 mL) and 33% HBr in acetic acid (120 mL). The solution was stirred and treated with bromine (11.1 mL, 0.21 mol) at such a rate that the bromine color was discharged rapidly, ca. 15 minutes. After an additional 10 minutes at room temperature, the solution was filtered and the filtrate concentrated *in vacuo* to give the bromoketone as an orange solid. The crude bromoketone was dissolved in dichloromethane and washed with 1N $NaHSO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give 68.8 g of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromoethanone as a yellow solid which was used directly in the next step.

Step 4: Preparation of 2-((4-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

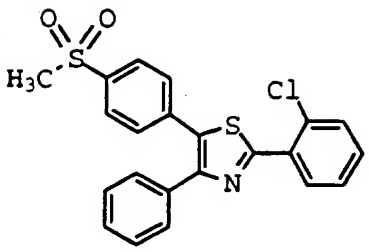
A solution of the bromoketone from Step 3 (2.51 g, 7.4 mmol) and 4-chlorophenoxy thioacetamide (1.27

g, 7.3 mmol) in 25 mL of acetonitrile was heated to reflux for 4 hours and concentrated in vacuo, the residue was taken up in ethyl acetate and washed successively with sat. aq. $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give the crude thiazole. The thiazole was purified by flash chromatography on silica gel, eluting with 5% ethyl acetate in hexane. The appropriate fractions were combined, concentrated *in vacuo* and then the crude solid was recrystallized from methanol to give pure thiazole (1.71 g, 61%): mp 91-95°C. ^1H NMR ($CDCl_3$) 300 MHz 7.49 (m, 2H), 7.22 (m, 6H), 6.99 (m, 4H), 5.37 (s, 2H), 2.49 (s, 3H); ^{19}F NMR ($CDCl_3$) -113.53 (m). High resolution field desorption mass spectrum Calc'd. for $C_{23}H_{17}ClFNOS_2Li$ (M^++Li): 448.0584. Found: 448.0554.

Step 5: Preparation of 2-((4-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A solution of the thiazole from Step 4 (1.39 g, 3.1 mmol) in 20 mL of dichloromethane was treated with *m*-chloroperbenzoic acid (MCPBA) (2.22 g, 6.4 mmol) at 0°C for 1 hour. The solution was washed with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a white foam that was purified by recrystallization from a mixture of dichloromethane and isooctane to give pure product (1.24 g, 83%): mp 140-43°C. ^1H NMR ($CDCl_3$) 300 MHz 7.87 (d, J= 8.5Hz, 2H), 7.53 (d, J=8.5Hz, 2H), 7.45 (m, 2H), 7.27 (d, J=9.2Hz, 2H), 6.99 (m, 4H), 5.38 (s, 2H), 3.08 (s, 3H); ^{19}F NMR ($CDCl_3$) -112.40 (m). Mass spectrum: M+H = 474.

Example 2



2-(2-Chlorophenyl)-4-phenyl-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-phenyl-3-(4-methylthiophenyl)propenoic acid:

A mixture of acetic anhydride (500 mL), 4-(methylthio)benzaldehyde (113.1 g, 0.743 mol), phenylacetic acid (101.2 g, 0.743 mol), and triethylamine (75.8 g, 0.75 mol) was heated to reflux for 5 hours. The reaction was cooled to 110°C, and water (500 mL) was added. A yellow precipitate formed, and after further cooling to room temperature, the solid was collected by filtration, washed with water, and recrystallized from isopropyl alcohol to give the diarylpropenoic acid as white needles (94.2 g, 57%): mp 167-169°C. ^{1}H NMR ($CDCl_3$) δ300 MHz 12.00 (br s, 1H), 7.91 (s, 1H), 7.38 (m, 3H), 7.24 (m, 2H), 7.00 (d, 2H), 6.99 (d, 2H), 2.43 (s, 3H).

Step 2: Preparation of 2-(4-methylthiophenyl)-1-phenylethanone:

The diarylpropenoic acid from Step 1 (12.27 g, 45.4 mmol) and triethylamine (8.44 g, 84 mmol) were dissolved in 110 mL of anhydrous toluene, cooled to 0°C and treated with diphenylphosphoryl azide (12.6 g, 83.4 mmol). The solution was maintained at 0°C for twenty minutes and warmed to room temperature for 2.5 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and

concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to reflux for 1.25 hours. *tert*-Butyl alcohol (5 mL, 53 mmol) was added to the solution, after an additional twenty minutes, concentrated hydrochloric acid (4 mL) was cautiously added and the reaction maintained at 90°C overnight (14 hours). After cooling the solution to room temperature, a white precipitate formed which was isolated by filtration, washed with cold ether, and air dried to yield the desired ketone which was crystallized from a mixture of dichloromethane and isooctane (5.16 g, 47%): mp 123-127°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.99 (d, J=7.3Hz, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 7.22 (d, J=8.4Hz 2H), 7.20 (d, J=8.5Hz, 2H), 4.24 (s, 2H), 2.46 (s, 3H).

Step 3: Preparation of 2-bromo-2-(4-methylthiophenyl)-1-phenylethanone:

A solution of the ketone from Step 2 (2.35 g, 9.7 mmol) in acetic acid (50 mL) and 33% HBr in acetic acid (4 mL) was treated with a 1.1 M solution of bromine in acetic acid (9 mL, 9.9 mmol) and then stirred at room temperature for 1 hour. The solution was diluted with dichloromethane and washed with 1N $NaHSO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give the bromoketone which was used directly in the next step (2.38 g, 76%): mp 93-95°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.97 (d, J=7.3Hz, 2H), 7.57 (m, 1H), 7.46 (m, 4H), 7.24 (d, J=8.5Hz, 2H), 6.35 (s, 1H), 2.47 (s, 3H).

Step 4: Preparation of 2-(2-chlorophenyl)-4-phenyl-5-(4-methylthiophenyl)thiazole:

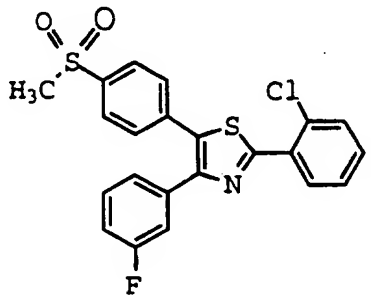
A solution of the bromoketone from Step 3 (2.38 g, 7.4 mmol) and 4-chlorothiobenzamide (1.29 g, 7.5 mmol) in 25 mL of acetonitrile was heated to reflux for 14 hours. The solution was cooled to room temperature and poured into 25 mL of methanol

whereupon crystals of pure diaryl thiazole formed which were isolated by filtration and air dried to afford the pure diaryl thiazole (2.01 g, 69%): mp 107-109.5°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.37 (m, 1H), 7.62 (m, 2H), 7.49 (d, J=7.7Hz, 1H), 7.32 (m, 7H), 7.22 (d, J=8.5Hz, 2H), 2.51 (s, 3H). Mass spectrum M+H =394.

Step 5: Preparation of 2-(2-chlorophenyl)-4-phenyl-5-(4-methylsulfonylphenyl)thiazole:

A solution of the diaryl thiazole from Step 4 (1.90 g, 4.8 mmol) in 10 mL of dichloromethane was treated with MCPBA (3.40 g, 9.9 mmol) at 0°C for 1 hour. The solution was washed with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid that was purified by flash chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to provide 1.5 g, 73% of pure product: mp 191.5-195°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.40 (m, 1H), 7.88 (d, J=8.5Hz, 2H), 7.51-7.62 (m, 5 H), 7.35-7.41 (m, 5H), 3.09 (s, 3H). High resolution mass spectrum Calc'd. for $C_{22}H_{16}ClNO_2S_2$: 425.0311. Found: 425.0315.

Example 3



2-(2-Chlorophenyl)-4-(3-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(3-fluorophenyl)-3-(4-methylthiophenyl)propenoic acid:

A mixture of acetic anhydride (60 mL), 4-(methylthio)benzaldehyde (4.99 g, 33 mmol), 3-fluorophenylacetic acid (5.08 g, 33 mmol), and triethylamine (3.98 g, 39 mmol) was heated to reflux for 4 hours. The reaction was cooled to 120°C, and water (120 mL) was added. A yellow precipitate formed and, after further cooling to room temperature, was collected by filtration, washed with water, and recrystallized from toluene to give the desired intermediate as a yellow solid (3.72 g, 39%): mp 184-187°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.92 (s, 1H), 7.35 (m, 1H), 7.26 (d, J=6.3Hz, 1H), 7.19 (d, J=7.7Hz, 1H) 7.00 (m, 5H), 2.44 and 2.36 (s, 3H); ^{19}F NMR ($CDCl_3$) -112.61 (m). Mass spectrum M+H=289.

Step 2: Preparation of 1-(3-fluorophenyl)-2-(4-methylthiophenyl)ethanone:

A solution of the intermediate from Step 1 (3.57 g, 12.4 mmol) and triethylamine (1.41 g, 13.9 mmol) dissolved in 35 mL of anhydrous toluene was cooled to 0°C and treated with diphenylphosphoryl azide (3.53 g, 12.8 mmol). The solution was maintained at 0°C for twenty minutes and warmed to room temperature for 3 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to reflux for 1 hour. *tert*-Butyl alcohol (4 mL, 42 mmol) was added to the reaction mixture. After an additional twenty minutes, concentrated hydrochloric acid (4 mL) was cautiously added and the reaction maintained at 80°C overnight (14 hours). After cooling the solution to room temperature, the mixture was poured into a separatory funnel and washed with water. The toluene layer was dried with anhydrous $MgSO_4$, filtered and

concentrated *in vacuo* to give a yellow powder. The crude solid was crystallized from a mixture of dichloromethane and isooctane to provide 1.30 g (40%) of the desired ketone: mp 116-120°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.77 (d, J=7.9 Hz, 1H), 7.68 (dt, J=9.4Hz 2.6Hz, 1H), 7.43 (m, 1H), 7.21-7.29 (m, 3H), 7.18 (d, J=8.3Hz, 2H), 4.22 (s, 2H), 2.46 (s, 3H); ^{19}F NMR ($CDCl_3$) -111.82 (m). Mass spectrum M+H=261.

Step 3: Preparation of 2-bromo-1-(3-fluorophenyl)2-(4-methylthiophenyl)ethanone:

A solution of the ketone from Step 2 (1.53 g, 5.9 mmol) in acetic acid (20 mL) and 33% HBr in acetic acid (0.5 mL) was treated with a 0.99 M solution of bromine in acetic acid (6.1 mL, 6.0 mmol) and stirred at room temperature for twenty minutes. The contents of the flask solidified and the precipitate was isolated by filtration. The filtrate solution was diluted with dichloromethane and washed with 1N $NaHSO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a solid that was combined with the original precipitate to provide 1.92 g (96%) of bromoketone: mp 101-104°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.73 (d, J=7.9Hz, 1H), 7.67 (dt, J=9.4Hz 2.3Hz, 1H), 7.41 (m, 3H), 7.24 (m, 3H), 6.27 (s, 1H), 2.47 (s, 3H); ^{19}F NMR ($CDCl_3$) -111.18 (m). Mass spectrum: M+H =340.

Step 4: Preparation of 2-(2-chlorophenyl)-4-(3-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

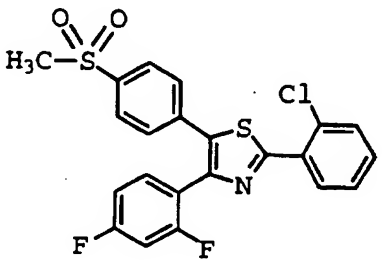
A solution of the bromoketone intermediate from Step 3 (0.77 g, 2.3 mmol) and 4-chlorothiobenzamide (0.40 g, 2.3 mmol) in 10 mL of acetonitrile was heated to reflux for 4 hours. The solution was cooled to room temperature and poured into 25 mL of methanol whereupon crystals of thiazole formed which were isolated by filtration and air dried to afford the pure thiazole (0.66 g, 71%): mp 106.5-108°C. ^{1}H NMR

($CDCl_3$) 300 MHz 8.37 (dd, J=7.4Hz 2.2Hz, 1H), 7.49 (d, J=7.0Hz, 1H), 7.21-7.42 (m, 9H), 7.00 (t, J=8.5Hz, 1H), 2.51 (s, 3H); ^{19}F NMR ($CDCl_3$) -113.10 (m). Mass spectrum: M^+=412.

Step 5: Preparation of 2-(2-chlorophenyl)-4-(3-fluorophenyl)-5-(4-methylsulfonylphenyl) thiazole:

A solution of the thiazole from Step 4 (610 mg, 1.48 mmol) in 15 mL of dichloromethane was treated with MCPBA (1.05 g) at room temperature for 72 hours. The solution was washed with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil that was crystallized from toluene to give yellow needles (320 mg, 48%): mp 133.5-135°C. ^1H NMR ($CDCl_3$) 300 MHz 8.39 (m, 1H), 7.91 (d, J=8.5Hz, 2H), 7.63 (d, J=8.5Hz 2H), 7.51 (m, 1H), 7.40 (m, 3H), 7.28 (m, 2H), 7.10 (m, 1H) 3.10 (s, 3H); ^{19}F NMR ($CDCl_3$) -112.70 (m). Mass spectrum: M^+=444.

Example 4



4-(2,4-Difluorophenyl)-2-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(2,4-difluorophenyl)-3-(4-methylthiophenyl)propenoic acid:

A mixture of acetic anhydride (50 mL), 4-(methylthio)benzaldehyde (3.75 g, 24.6 mmol), 2,4-difluorophenylacetic acid (4.41 g, 24.6 mmol), and triethylamine (2.80 g, 27.7 mmol) was heated to reflux

for 3.5 hours. The reaction was cooled to 90°C, and water (100 mL) was added. A yellow oil formed that solidified upon stirring. The solid was collected by filtration, and dissolved in ethyl acetate, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The solid thus obtained was recrystallized from toluene to give the desired acid (3.18 g, 42%): mp 165-171°C. ^1H NMR (acetone-d_6) 300 MHz 7.95 (s, 1H), 7.08-7.18 (m, 7H), 2.47 and 2.31 (s, 3H); ^{19}F NMR (acetone-d_6) -110.81 (m) -111.75 (m). Mass spectrum: M+H=306.

Step 2: Preparation of 1-(2,4-difluorophenyl)-2-(4-methylthiophenyl)ethanone:

A solution of the acid from Step 1 (3.11 g, 10.2 mmol) and triethylamine (1.23 g, 10.8 mmol) dissolved in 15 mL of anhydrous toluene, was cooled to 0°C and treated with diphenylphosphoryl azide (2.98 g, 10.8 mmol). The solution was maintained at 0°C for twenty minutes and warmed to room temperature for 1 hour. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was diluted with an additional 10 mL of toluene and heated to 90°C for 1.5 hours. *tert*-Butyl alcohol (4 mL, 42 mmol) was added to the reaction mixture. After an additional twenty minutes, concentrated hydrochloric acid (4 mL) was cautiously added and the reaction maintained at 90°C overnight (16 hours). After cooling the solution to room temperature, the mixture was diluted with ethyl acetate, and washed with water. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. The crude solid was crystallized from a mixture of ethyl acetate and hexane to provide the desired ketone (2.19 g, 77%): mp 82-88.5°C. ^1H NMR ($CDCl_3$) 300 MHz 7.91 (q, J=6.0Hz, 1H), 7.22 (d, J=8.1Hz, 2H), 7.15 (d, J=8.5Hz, 2H),

6.82-6.97 (m, 2H), 4.21 (d, J=2.6Hz, 2H), 2.46 (s, 3H); ^{19}F NMR ($CDCl_3$) -101.74 (m), -104.15 (m). Mass spectrum: M^+=278 .

Step 3: Preparation of 1-(2,4-difluorophenyl)-2-bromo-2-(4-methylthiophenyl)ethanone:

A solution of the ketone intermediate from Step 2 (2.05 g, 7.4 mmol) in acetic acid (30 mL) and 33% HBr in acetic acid (0.5 mL) was treated with a 0.99 M solution of bromine in acetic acid (7.6 mL, 7.5 mmol) and stirred at room temperature for 1 hour. The solution was concentrated *in vacuo* and the residue was taken up in dichloromethane, washed with 1N $NaHSO_3$, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a brown solid (2.39 g, 90%) that was unstable and used directly in the next step without further purification. ^1H NMR ($CDCl_3$) 300 MHz 7.94 (q, J=6.3Hz, 1H), 7.37 (d, J=8.5Hz, 2H), 7.21 (d, J=8.5Hz, 2H), 6.97 (m, 1H), 6.84 (m, 1H), 6.28 (s, 1H), 2.46 (s, 3H); ^{19}F NMR ($CDCl_3$) -100.31 (m), -103.50 (m). Mass spectrum: M+H = 358.

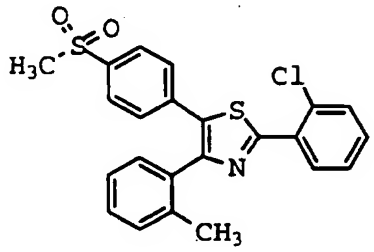
Step 4: Preparation of 4-(2,4-difluorophenyl)-2-(2-chlorophenyl)-5-(4-methylthiophenyl)thiazole:

A solution of the bromoketone intermediate from Step 3 (0.49 g, 1.3 mmol) and 4-chlorothiobenzamide (0.24 g, 1.4 mmol) in 5 mL of acetonitrile was heated to reflux for 3 hours. The solution was cooled to room temperature and poured into 20 mL of methanol, chilled with an ice bath, whereupon crystals of the thiazole formed which were isolated by filtration and air dried (0.31 g, 52%): mp 103-105°C. ^1H NMR ($CDCl_3$) 300 MHz 8.31 (m, 1H), 7.50-7.60 (m, 2H), 7.36 (m, 2H), 7.23 (d, J=8.5Hz, 2H), 7.19 (d, J=8.5Hz, 2H), 6.94 (t, J=8.5Hz, 1H), 6.83 (t, J=9.2Hz, 1H) 2.48 (s, 3H). ^{19}F NMR ($CDCl_3$) -108.50 (m), -109.49 (m). Mass spectrum M+H=430.

Step 5: Preparation of 4-(2,4-difluorophenyl)-2-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A solution of the thiazole from Step 4 (260 mg, 0.60 mmol) in 4 mL of dichloromethane was treated with MCPBA (0.42 g) at room temperature for 1.5 hours. The solution was diluted with additional dichloromethane, washed with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid that was recrystallized from a mixture of dichloromethane and isooctane to give white needles (250 mg, 89%): mp 166-169°C. ^1H NMR ($CDCl_3$) 300 MHz 8.34 (m, 1H), 7.88 (d, J=8.5Hz, 2H) 7.65 (q, J=6.6Hz, 1H), 7.55 (d, J=8.1Hz, 2H), 7.41 (m, 2H), 7.26 (s, 1H), 6.99 (t, J=8.1Hz, 1H), 6.83 (t, J=8.9Hz, 1H) 3.08 (s, 3H); ^{19}F NMR ($CDCl_3$) -108.40 (m), -108.69 (m). Mass spectrum: M+H=462.

Example 5



2-(2-Chlorophenyl)-4-(2-methylphenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(2-methylphenyl)-3-(4-methylthiophenyl)propenoic acid:

A mixture of acetic anhydride (160 mL), 4-(methylthio)benzaldehyde (25.32 g, 166 mmol), 2-methylphenylacetic acid (24.95 g, 166 mmol), and triethylamine (17.89 g, 176 mmol) was heated to reflux for 2.67 hours. The reaction was cooled to 100°C, and water (200 mL) was added. A clear oil formed that solidified upon chilling with an ice bath. The solid

was collected by filtration, and recrystallized from a mixture of ethyl acetate and isooctane to give the desired acid in two crops (18.6 g, 39%): mp 134-137°C. ^{1}H NMR ($CDCl_3$) 300 MHz 9.80 (br s, 1H), 7.91 (s, 1H), 7.28 (m, 3H), 7.12 (d, J=7.5Hz, 1H), 7.00 (d, J=8.5Hz, 2H), 6.93 (d, J=8.5Hz, 2H), 2.42 (s, 3H), 2.16 (s, 3H). High resolution mass spectrum Calc'd. for $C_{17}H_{16}O_2S$: 284.0871. Found: 284.0863.

Step 2: Preparation of 1-(2-methylphenyl)2-(4-methylthiophenyl)ethanone:

A solution of the acid from Step 1 (8.29 g, 29.2 mmol) and triethylamine (3.46 g, 34.2 mmol) dissolved in 30 mL of anhydrous toluene, was cooled to 0°C and treated with diphenylphosphoryl azide (8.23 g, 29.9 mmol). The solution was maintained at 0°C for 45 minutes and warmed to room temperature for 3.75 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to 110°C for 1 hour. *tert*-Butyl alcohol (6 mL, 63 mmol) was added to the reaction mixture, after an additional twenty minutes, concentrated hydrochloric acid (2.6 mL) was cautiously added and the reaction maintained at 90°C overnight (16 hours). After cooling the solution to room temperature, the mixture was concentrated *in vacuo* and the residue was taken up in ethyl acetate, washed successively with water, sat. aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid (6.44 g, 86%): mp 54-61°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.69 (d, J=7.7Hz, 1H), 7.36 (m, 1H), 7.20-7.26 (m, 4H), 7.16 (d, J=8.5Hz, 2H), 4.17 (s, 2H), 2.46 (s, 3H), 2.44 (s, 3H). Mass spectrum M+H=257.

Step 3: Preparation of 2-bromo-1-(2-methylphenyl)-2-(4-methylthiophenyl)ethanone:

A solution of the ketone from Step 2 (5.92 g, 23.1 mmol) in acetic acid (50 mL) and 33% HBr in acetic acid (2 mL) was treated with a 1.1 M solution of bromine in acetic acid (21.7 mL, 23.8 mmol) and stirred at room temperature for 2 hours. The solution was concentrated *in vacuo* and the residue taken up in dichloromethane, washed with 1N $NaHSO_3$ and sat. aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid which was used directly in the next step without further purification (5.97 g, 77%): mp 85-89°C . ^1H NMR ($CDCl_3$) 300 MHz 7.56 (d, J=7.9Hz, 1H), 7.41 (d, J=8.5Hz, 2H), 7.37 (d, J=7.7Hz, 1H), 7.22 (m, 4H), 6.18 (s, 1H), 2.47 (s, 3H), 2.44 (s, 3H). Mass spectrum M+H=341.

Step 4: Preparation of 2-(2-chlorophenyl)-4-(2-methylphenyl)-5-(4-methylthiophenyl)thiazole:

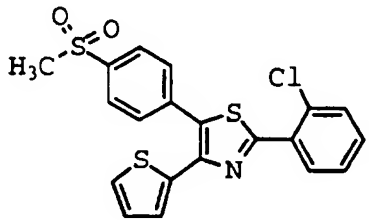
A solution of the bromoketone intermediate from Step 3 (0.68 g, 2.03 mmol) and 4-chlorothiobenzamide (0.34 g, 1.98 mmol) in 10 mL of acetonitrile was heated to reflux for 16 hours. The solution was cooled to room temperature and poured into 30 mL of methanol, chilled with an ice bath whereupon crystals of pure thiazole formed which were isolated by filtration and air dried to afford the desired thiazole (220 mg, 27%): mp 116-119°C. ^1H NMR ($CDCl_3$) 300 MHz 8.33 (m, 1H), 7.50 (m, 1H), 7.16-7.36 (m, 8H), 7.12 (d, J=8.7Hz, 2H), 2.46 (s, 3H), 2.18 (s, 3H). Mass spectrum: M^+=407.

Step 5: Preparation of 2-(2-chlorophenyl)-4-(2-methylphenyl)-5-(4-methylsulfonylphenyl)thiazole:

A solution of the thiazole from Step 4 (220 mg, 0.54 mmol) in 5 mL of dichloromethane was treated with MCPBA (390 mg, 1.13 mmol) at room temperature for 55 minutes. The solution was diluted with additional dichloromethane, washed with 10% aq. $NaHSO_3$, and 10%

Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow powder that was recrystallized from a mixture of dichloromethane and isooctane to give a yellow solid (44 mg, 18%): mp 156.5-157°C. ^1H NMR ($CDCl_3$) 300 MHz 8.38 (m, 1H), 7.79 (d, J=8.6Hz, 2H), 7.52 (m, 1H), 7.46 (d, J=8.3Hz, 2H), 7.39 (m, 2H), 7.21-7.34 (m, 4H), 3.05 (s, 3H), 2.19 (s, 3H). High resolution mass spectrum Calc'd. for $C_{23}H_{18}ClNO_2S_2$: 439.0468. Found: 439.0476.

Example 6



2-(2-Chlorophenyl)-5-(4-methylsulfonylphenyl)-4-(2-thienyl)thiazole

Step 1: Preparation of 3-(4-methylthiophenyl)-2-(2-thienyl)propenoic acid:

A mixture of acetic anhydride (90 mL), 4-(methylthio)benzaldehyde (13.17 g, 82.2 mmol), 2-(2-thienyl)acetic acid (12.09 g, 83.3 mmol), and triethylamine (8.60 g, 85 mmol) was heated to reflux for 4 hours. The reaction was cooled to 85°C, and water (80 mL) was added. A brown solid was isolated by filtration and air dried to afford the propenoic acid (8.48 g, 37%): mp 201-206°C. ^1H NMR (DMSO-d_6) 300 MHz 12.80 (br s, 1H), 7.77 (s, 1H), 7.60 (d, J=5.2Hz, 1H), 7.09 (m, 5H), 6.92 (d, J=3.3Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (DMSO-d_6) 168.24,141.60, 141.30, 136.84, 131.08, 130.86, 128.46, 127.86, 125.51, 125.28, 14.52. Mass spectrum: M+H=277.

Step 2: Preparation of 2-(4-methylthiophenyl)-1-(2-thienyl)ethanone:

A solution of the propenoic acid intermediate from Step 1 (8.13 g, 29.4 mmol) and triethylamine (3.33 g, 32.9 mmol) dissolved in 40 mL of anhydrous toluene, was cooled to 0°C and treated with diphenylphosphoryl azide (8.15 g, 29.6 mmol). The solution was maintained at 0°C for twenty minutes and warmed to room temperature for 4 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to 110°C for 1.5 hours. *tert*-Butyl alcohol (8.5 mL, 85.6 mmol) was added to the reaction mixture. After an additional twenty minutes, concentrated hydrochloric acid (5 mL) was cautiously added and the reaction maintained at 90°C overnight (16 hours). After cooling with an ice bath, a solid separated and was isolated by filtration. The filtrate was concentrated *in vacuo* and the residue taken up in dichloromethane washed with water, sat. aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a brown solid. The two batches of solid were combined and recrystallized from a mixture of dichloromethane and isooctane to give the ketone as a light brown solid (3.02 g, 41 %): mp 100-101°C. ^1H NMR ($CDCl_3$) 300 MHz 7.76 (dd, J= 3.8Hz, 1.1Hz, 1H), 7.63 (dd, J=4.9Hz, 1.1Hz, 1H), 7.22 (s, 4H), 7.12 (dd, J=4.9Hz, 3.8Hz, 1H), 4.15 (s, 2H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$) 300 MHz 190.28, 143.80, 137.22, 134.05, 132.61, 131.18, 129.89, 128.19, 127.08, 45.85, 15.99. Mass spectrum: M+H=249.

Step 3: Preparation of 2-bromo-2-(4-methylthiophenyl)-1-(2-thienyl)ethanone:

A solution of the ketone from Step 2 (3.02 g, 12 mmol) in acetic acid (70 mL) and 33% HBr in acetic

acid (4 mL) was treated with a 0.99 M solution of bromine in acetic acid (13 mL, 12.8 mmol) and stirred at room temperature for 2 hours. The solution was concentrated *in vacuo* and the residue taken up in dichloromethane, washed with 1N $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the bromoketone as a brown solid (2.95 g, 74%): mp 60-64.5°C. ^1H NMR ($CDCl_3$) 300 MHz 7.75 (d, J= 4.0Hz, 1H), 7.66 (d, J=4.8Hz, 1H), 7.45 (d, J=8.3Hz, 2H), 7.22 (d, J=8.3Hz, 2H), 7.10 (m, 1H), 6.19 (s, 1H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) 300 MHz 184.08, 140.67, 140.62, 135.39, 133.53, 132.26, 129.52, 128.53, 126.50, 51.30, 15.42. Mass spectrum: M+H=328.

Step 4: Preparation of 2-(2-chlorophenyl)-5-(4-methylthiophenyl)-4-(2-thienyl)thiazole:

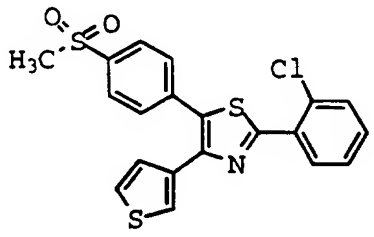
A solution of the bromoketone from Step 3 (340 mg, 1.0 mmol) and 4-chlorothiobenzamide (180 mg, 1.0 mmol) in 3 mL of acetonitrile was heated to reflux for 5 hours. The solution was cooled to room temperature, poured into 30 mL of methanol and chilled with an ice bath whereupon crystals of pure thiazole formed which were isolated by filtration and air dried to afford the desired thiazole (180 mg, 42%) which was used directly in the next step. ^1H NMR ($CDCl_3$) 300 MHz 8.39 (d, J=6.2Hz, 1H), 7.22-7.51 (m, 8H), 7.14 (d, J=3.4Hz, 1H), 6.94 (m, 1H), 2.54 (s, 3H).

Step 5: Preparation of 2-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)-4-(2-thienyl)thiazole:

A solution of the thiazole from Step 4 (140 mg, 0.35 mmol) in 3 mL of dichloromethane was treated with MCPBA (250 mg, 0.72 mmol) at room temperature for 2 hours. The solution was diluted with additional dichloromethane, washed with 10% aq. $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a green solid that was

purified by flash chromatography on silica gel eluting with hexane ethyl acetate to give white solid (100 mg, 67%): mp 171-174°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.41 (dd, J=7.3Hz 1.8Hz, 1H), 7.99 (d, J=8.3Hz, 2H), 7.77(d, J=8.5Hz, 2H), 7.50 (d, J=7.7Hz, 1H), 7.40 (m, 2H), 7.30 (d, J=4.0Hz, 1H), 7.09 (d, J=3.6Hz, 1H), 6.95 (m, 1H), 3.12 (s, 3H). High resolution mass spectrum Calc'd. for $C_{20}H_{15}ClNO_2S_3$ (M+H): 431.9953. Found: 431.9954.

Example 7



2-(2-Chlorophenyl)-5-(4-methylsulfonylphenyl)-4-(3-thienyl)thiazole

Step 1: Preparation of 3-(4-methylthiophenyl)-2-(3-thienyl)propenoic acid:

A mixture of acetic anhydride (100 mL), 4-(methylthio)benzaldehyde (11.06 g, 72.7 mmol), 3-thiopheneacetic acid (10.33 g, 72.7 mmol), and triethylamine (7.68 g, 75.9 mmol) was heated to reflux for 3 hours. The reaction was cooled to 90°C, and water (100 mL) was added. A white solid separated from the solution was isolated by filtration and air dried to afford the acid (11.0 g, 55%): mp 184-189°C. ^{1}H NMR (DMSO-d_6) δ 300 MHz 12.61 (br s, 1H), 7.69 (s, 1H), 7.54 (d, J=4.7Hz, 1H), 7.31 (s, 1H), 7.08 (d, J=8.7Hz, 2H), 7.02 (d, J=8.7Hz, 2H), 6.89 (d, J=5.1Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (DMSO-d_6) 168.63,140.70, 139.70, 136.22, 131.29, 130.89, 129.35, 127.74,

126.57, 125.53, 125.06, 14.57. Mass spectrum: M+H = 277.

Step 2: Preparation of 2-(4-methylthiophenyl)-1-(3-thienyl)ethanone:

A solution of the acid from Step 1 (7.20 g, 26.1 mmol) and triethylamine (2.83 g, 28 mmol) dissolved in 30 mL of anhydrous toluene, was cooled to 0°C and treated with diphenylphosphoryl azide (7.72 g, 28.1 mmol). The solution was maintained at 0°C for thirty minutes and warmed to room temperature for 3 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to 100°C for 1.5 hours. *tert*-Butyl alcohol (3 mL, 31.8 mmol) was added to the reaction mixture. After an additional fifteen minutes, concentrated hydrochloric acid (2 mL) was cautiously added and the reaction maintained at 80°C for 72 hours. After cooling with an ice bath, a solid separated and was isolated by filtration. The filtrate was concentrated *in vacuo* and the residue taken up in dichloromethane, washed with water, sat. aq. $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a brown solid. The two batches of solid were combined and recrystallized from a mixture of ethyl acetate and hexane to give a light brown solid. Washing the solid with ether afforded pure white ketone (5.0 g, 77%): mp 119-122°C. ^1H NMR ($CDCl_3$) 300 MHz 8.08 (m, 1H), 7.55 (d, J=5.2Hz, 1H), 7.30 (m, 1H), 7.21 (m, 4H), 4.13 (s, 2H), 2.46 (s, 3H). Mass spectrum: M+H = 249.

Step 3: Preparation of 2-bromo-2-(4-methylthiophenyl)-1-(3-thienyl)ethanone:

A solution of the ketone from Step 2 (4.0 g, 16.1 mmol) in acetic acid (100 mL) and 33% HBr in acetic acid (5 mL) was treated with a 0.99 M solution of

bromine in acetic acid (16.5 mL, 16.3 mmol) and stirred at room temperature for 1 hour. The solution was concentrated *in vacuo* and the residue taken up in dichloromethane, washed with 1N $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a gray solid which was recrystallized from a mixture of ethyl acetate and isooctane to provide the bromoketone intermediate (4.22 g, 80%): mp 74-76.5°C. Mass spectrum: M+H = 328.

Step 4: Preparation of 2-(2-chlorophenyl)-5-(4-methylthiophenyl)-4-(3-thienyl)thiazole:

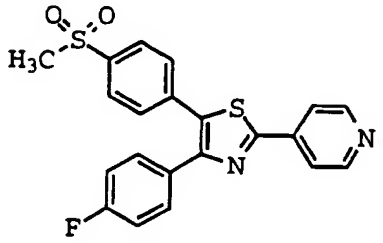
A solution of the bromoketone from Step 3 (330 mg, 1.0 mmol) and 4-chlorothiobenzamide (180 mg, 1.0 mmol) in 10 mL of acetonitrile was heated to reflux for 15 hours. The solution was cooled to room temperature and poured into 30 mL of methanol, chilled with an ice bath, whereupon crystals of pure thiazole formed which were isolated by filtration and air dried to afford the thiazole which was used directly in the next step (230 mg, 58%): mp 102-103.5°C. ^1H NMR ($CDCl_3$) 300 MHz 8.39 (d, 1H), 7.57 (m, 1H), 7.49 (d, 1H), 7.39 (m, 4H), 7.26 (m, 4H), 2.53 (s, 3H). Mass spectrum: M+H=401.

Step 5: Preparation of 2-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)-4-(3-thienyl)thiazole:

A solution of the thiazole from Step 4 (180 mg, 0.45 mmol) in 2 mL of dichloromethane was treated with MCPBA (330 mg, 0.95 mmol) at room temperature for 4 hours. The solution was diluted with additional dichloromethane, washed with 10% aq. $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid that was purified by flash chromatography on silica gel, eluting with hexane and ethyl acetate to give a white solid (60 mg, 32%) ^1H NMR ($CDCl_3$) 300 MHz 8.39 (m,

1H), 7.94 (d, J=8.5Hz, 2H), 7.70 (d, J=8.5Hz, 2H), 7.56 (m, 2H), 7.39 (m, 2H), 7.28 (m, 1H), 7.17 (d, J=5.0Hz, 1H), 3.11 (s, 3H). Mass spectrum: M+H = 432.

Example 8



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(4-pyridyl)thiazole

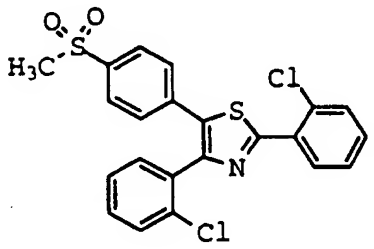
Step 1: Preparation of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(4-pyridyl)thiazole:

A solution of the intermediate from Example 1, Step 3, 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromoethanone, (1.58 g, 4.66 mmol) and thioisonicotinamide (670 mg, 4.84 mmol) in 25 mL of acetonitrile was heated to reflux for 23 hours. The solution was filtered, concentrated *in vacuo* and the residue taken up in dichloromethane. The dichloromethane solution was washed with sat. aq. $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil that was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane to provide the desired thiazole as an oil that solidified upon standing (640 mg, 36%): mp 107-109°C. ^1H NMR ($CDCl_3$) 300 MHz 8.75 (br s, 2H), 7.85 (d, J=5.9 Hz, 2H), 7.56 (m, 2H), 7.26 (d, J=8.5 Hz, 2H), 7.22 (d, J=8.5 Hz, 2H), 7.01 (t, J=8.5 Hz, 2H), 2.50 (s, 3H); ^{19}F NMR ($CDCl_3$) -113.23 (m). High resolution mass spectrum Calc'd. for $C_{21}H_{15}FN_2S_2$: 379.0661. Found: 379.0691.

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(4-pyridyl)thiazole:

A solution of the thiazole from Step 1 (450 mg, 1.19 mmol) in 10 mL of dichloromethane was treated with MCPBA (850 mg, 2.46 mmol) at room temperature for 2.5 hours. The solution was diluted with additional dichloromethane, washed with 10% aq. $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid that was purified by recrystallization from a mixture of dichloromethane, ethanol and isooctane to provide the pure product (310 mg, 63%): mp 171-176°C. ^1H NMR ($CDCl_3$) 300 MHz 8.25 (d, J=7.2Hz, 2H), 7.90 (m, 4H), 7.56 (d, J=8.7 Hz, 2H), 7.50 (m, 2H), 7.04 (t, J=8.7 Hz, 2H), 3.09 (s, 3H). ^{19}F NMR ($CDCl_3$) -111.83 (m). High resolution mass spectrum Calc'd. for $C_{21}H_{15}FN_2O_2S_2$: 410.0559. Found: 410.0576.

Example 9



2-(2-Chlorophenyl)-4-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(2-chlorophenyl)-3-(4-methylthiophenyl)propenoic acid:

A mixture of acetic anhydride (170 mL), 4-(methylthio)benzaldehyde (20.93 g, 137 mmol), 2-chlorophenylacetic acid (23.43 g, 137 mmol), and triethylamine (14.97 g, 147 mmol) was heated to reflux for 2 hours. The reaction was cooled to 90°C, and

water (180 mL) was added. A yellow solid that separated from the solution was isolated by filtration and air dried to afford the desired acid. The acid was recrystallized from a mixture of ethyl acetate and isooctane to afford 24.62 g (59%): mp 159-164°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.97 (s, 1H), 7.48 (d, J=7.9Hz, 1H), 7.17-7.35 (m, 3H), 7.02 (d, J=8.7Hz 2H), 6.97 (d, J=8.7Hz, 2H), 2.43 (s, 3H). High resolution mass spectrum Calc'd. for $C_{16}H_{13}ClO_2S$: 304.0325. Found: 304.0334.

Step 2: Preparation of 1-(2-chlorophenyl)2-(4-methylthiophenyl)ethanone:

A solution of the acid from Step 1 (17.88 g, 58.7 mmol) and triethylamine (9.53 g, 94.2 mmol) was dissolved in 50 mL of anhydrous toluene, cooled to 0°C and treated with diphenylphosphoryl azide (16.46 g, 59.8 mmol). The solution was maintained at 0°C for 36 minutes and warmed to room temperature for 4 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo*. The remaining toluene solution was heated to 110°C for 1 hour. *tert*-Butyl alcohol (7 mL, 74 mmol) was added to the reaction mixture. After an additional twenty minutes, concentrated hydrochloric acid (5 mL) was cautiously added and the reaction maintained at 90°C for 16 hours. The solution was concentrated *in vacuo* and the residue taken up in ethyl acetate, washed with water, sat. aq. $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to provide the ketone as an orange oil (14.62 g, 90%) that was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) 300 MHz 7.40-7.10 (m, 8H), 4.20 (s, 2H), 2.46 (s, 3H).

Step 3: Preparation of 2-bromo-1-(2-chlorophenyl)-2-(4-methylthiophenyl)ethanone:

A solution of the ketone from Step 2 (13.82 g, 49.9 mmol) in acetic acid (80 mL) and 33% HBr in acetic acid (4 mL) was treated with a 1.1 M solution of bromine in acetic acid (46.8 mL, 51.3 mmol) and stirred at room temperature for 1.5 hours. The solution was concentrated in vacuo and the residue taken up in dichloromethane, washed with 1N $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give the bromoketone as an orange solid (6.07 g, 34%) of sufficient purity to be used directly in the next step without further purification: mp 93-99°C. ^1H NMR ($CDCl_3$) 300 MHz 7.37-7.43 (m, 5H), 7.41 (m, 1H), 7.22 (d, J=8.5Hz, 2H), 6.21 (s, 1H), 2.47 (s, 3H). Mass spectrum: M+H = 357.

Step 4: Preparation of 2-(2-chlorophenyl)-4-(2-chlorophenyl)-5-(4-methylthiophenyl)thiazole:

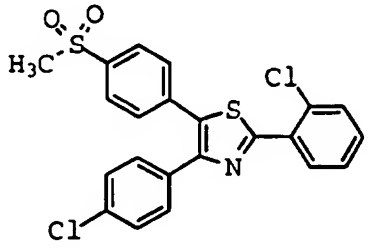
A solution of the bromoketone from Step 3, (1.14 g, 3.2 mmol) and 2-chlorothiobenzamide (550 mg, 3.2 mmol) in 10 mL of acetonitrile was heated to reflux for 16 hours. The solution was cooled to room temperature and poured into methanol. This solution was chilled whereupon a yellow solid separated that was isolated by filtration. The solid was air dried to provide pure thiazole (440 mg, 32%): mp 116-120°C. ^1H NMR ($CDCl_3$) 300 MHz 8.33 (m, 1H), 7.29-7.52 (m, 7H), 7.19(d, J=8.3Hz, 2H), 7.14 (d, J=8.5Hz, 2H), 2.46 (s, 3H). Mass spectrum: M^+=427.

Step 5: Preparation of 2-(2-chlorophenyl)-4-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A solution of the thiazole from Step 4 (440 mg, 1.02 mmol) in 5 mL of dichloromethane was treated with MCPBA (720 mg, 2.08 mmol) at room temperature for 0.9 hour. The solution was diluted with additional dichloromethane, washed with 10% aq. $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and

concentrated *in vacuo* to give a yellow solid. The solid was recrystallized from a mixture of dichloromethane and isooctane to provide pure product (270 mg, 57%): mp 143-147°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.36 (m, 1H), 7.82 (d, J=8.3Hz, 2H), 7.52 (m, 1H), 7.45 (m, 4H), 7.38 (m, 4H), 3.05 (s, 3H). High resolution mass spectrum Calc'd. for $C_{22}H_{15}Cl_2NO_2S_2$: 458.9921. Found: 458.9903.

Example 10



2-(2-Chlorophenyl)-4-(4-chlorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(4-chlorophenyl)-3-(4-methylthiophenyl)propenoic acid:

A mixture of acetic anhydride (80 mL), 4-(methylthio)benzaldehyde (9.81 g, 61.2 mmol), 4-chlorophenylacetic acid (12.03 g, 70.5 mmol), and triethylamine (7.49 g, 7.42 mmol) was heated to reflux for 7 hours. The reaction was cooled to 90°C, and water (100 mL) was added. A yellow solid separated from the solution which was isolated by filtration and air dried to afford the desired acid. The acid was recrystallized from toluene (9.59 g, 51%): mp 185-187°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.91 (s, 1H), 7.35 (d, J=8.3Hz, 1H), 7.17-7.35 (m, 3H), 7.03 (d, 2H), 7.00 (d, J=8.7Hz, 2H), 2.44 and 2.36 (s, 3H). Mass spectrum: M+H=305.

Step 2: Preparation of 1-(4-chlorophenyl)-2-(4-methylthiophenyl)ethanone:

The acid from Step 1 (9.01 g, 29.6 mmol) and triethylamine (3.03 g, 29.9 mmol) were dissolved in 45 mL of anhydrous toluene, cooled to 0°C and treated with diphenylphosphoryl azide (8.22 g, 29.9 mmol). The solution was maintained at 0°C for 10 minutes and warmed to room temperature for 2 hours. The reaction was poured into water, extracted with ether, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to 90°C for 15 minutes. *tert*-Butyl alcohol (10 mL) was added to the reaction mixture. After an additional twenty minutes, concentrated hydrochloric acid (8 mL) was cautiously added and the reaction maintained at 90°C for 15 minutes. The solution was cooled to room temperature and a precipitate formed that was isolated by filtration, washed with ether and air dried to provide the desired ketone as a white solid (2.43 g, 30%): mp 143-147.5°C. ^1H NMR ($CDCl_3$) 300 MHz 8.08 (d, J=8.8Hz, 2H), 7.55 (d, J=8.5Hz, 2H), 7.24 (m, 4H), 4.35 (s, 2H), 2.05 (s, 3H). Mass spectrum: M+H=277.

Step 3: Preparation of 2-bromo-1-(4-chlorophenyl)-2-(4-methylthiophenyl)ethanone:

A solution of the ketone from Step 2 (2.04 g, 7.37 mmol) in acetic acid (15 mL) and 48% HBr in acetic acid (2 mL) was treated with a 0.99 M solution of bromine in acetic acid (7.6 mL, 7.5 mmol) and stirred at room temperature for 2.25 hours. The desired product precipitated from the solution, was isolated by filtration and air dried to provide the bromoketone intermediate for use in the next step (0.91 g, 35%): mp 114-115°C. ^1H NMR ($CDCl_3$) 300 MHz 7.90 (d, J=8.8Hz, 2H), 7.40 (d, J=8.5Hz, 4H), 7.23 (d, J=8.5Hz, 2H), 6.28 (s, 1H), 2.47 (s, 3H); ^{13}C NMR

($CDCl_3$) 400 MHz 189.76, 140.68, 140.30, 132.44, 131.88, 130.54, 129.51, 129.19, 126.51, 50.57, 15.33. High resolution mass spectrum Calc'd. for $C_{15}H_{12}BrClOS$: 353.9481. Found: 353.9516.

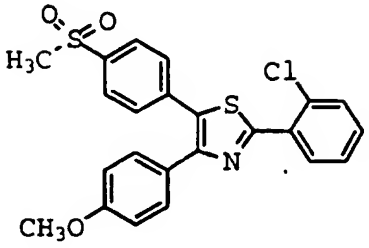
Step 4: Preparation of 2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(4-methylthiophenyl)thiazole:

A solution of the bromoketone intermediate from Step 3, (890 mg, 2.5 mmol) and 2-chlorothiobenzamide (430 mg, 2.5 mmol) in 15 mL of acetonitrile was heated to reflux for 16 hours. The solution was diluted with ethyl acetate washed with sat. aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a white solid. The crude material was purified by flash chromatography on silica gel eluting with 8% ethyl acetate in hexane to give the desired thiazole as a white solid (370 mg, 34%): mp 122-124°C. ^1H NMR ($CDCl_3$) 300 MHz 8.37 (m, 1H), 7.56 (d, J=8.5Hz, 2H), 7.50 (m, 1H), 7.20-7.39 (m, 8H), 2.51 (s, 3H). Mass spectrum: M+H = 429.

Step 5: Preparation of 2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A solution of the thiazole from Step 4 (300 mg, 0.7 mmol) in 10 mL of dichloromethane was treated with MCPBA (530 mg, 1.5 mmol) at room temperature for 1 hour. The solution was diluted with additional dichloromethane, washed successively with 10% aq. $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. The solid was recrystallized from a mixture of dichloromethane and isooctane to provide pure product (180 mg, 56%): mp 177-179°C. ^1H NMR ($CDCl_3$) 300 MHz 8.37 (m, 1H), 7.91 (d, J=8.7Hz, 2H), 7.62 (d, J=8.5Hz, 2H), 7.50 (d, 3H), 7.40 (m, 2H), 7.34 (d, J=8.7Hz, 2H), 3.10 (s, 3H). High resolution mass spectrum Calc'd. for $C_{22}H_{15}Cl_2NO_2S_2$: 458.9921. Found: 458.9922.

Example 11



2-(2-Chlorophenyl)-4-(4-methoxyphenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(4-methoxyphenyl)-3-(4-methylthiophenyl)propenoic acid:

Acetic anhydride (350 mL), 4-(methylthio)benzaldehyde (61.6 g, 0.61 mol), 4-methoxyphenylacetic acid (100.0 g, 0.60 mol) and triethylamine (68.1 g, 0.67 mol) were heated to reflux for 4 hours. The reaction was cooled to 110°C, and water (350 mL) was added. This caused the solution to reflux vigorously and the temperature rose to 135°C. A yellow precipitate formed and, after cooling to room temperature, was collected by filtration, washed with water and air dried. The product was crystallized from ethyl acetate/ethanol to give the desired acid as bright yellow needles (127.6 g, 71%): mp 174-177°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.89 (s, 1H), 7.16 (d, J=8.6Hz, 2H), 7.02 (s, 4H), 6.92 (d, J=8.6Hz, 2H), 3.84 (s, 3H), 2.43 (s, 3H). Mass spectrum: M+H = 300.

Step 2: Preparation of 1-(4-methoxyphenyl)-2-(4-methylthiophenyl)ethanone:

The acid from Step 1 (23.0 g, 76.6 mmol) was added to anhydrous toluene (100 mL) and triethylamine (7.98 g, 79 mmol). After cooling to 0°C, diphenylphosphoryl azide (21.27 g, 79 mmol) was added, the solution was stirred at 0°C for twenty minutes at room temperature for 2.50 hours. The mixture was

poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo*. The remaining toluene solution was heated to 100°C whereupon a vigorous evolution of gas occurred. After 1.25 hours, *tert*-butyl alcohol (8.2 mL) was added to the reaction, and after an additional twenty minutes, concentrated hydrochloric acid (7 mL) was added. The reaction was heated at 75°C overnight (14 hours) and after cooling a white precipitate formed. The precipitate was filtered, washed with cold ether, and air dried to yield the light yellow ketone (19.3 g, 93%): mp 134.5-138°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.99 (d, J=8.9Hz, 2H), 7.20 (m, 4H), 6.93 (d, J=8.9Hz, 2H), 4.18 (s, 2H), 3.84 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) 300 MHz 196.18, 163.65, 136.87, 131.92, 131.00, 129.97, 129.64, 127.15, 113.92, 55.58, 44.78, 16.11. Mass spectrum: M+H = 273.

Step 3: Preparation of 2-bromo-1-(4-methoxyphenyl)-2-(4-methylthiophenyl)ethanone:

The ketone from Step 2 (19.3 g, 71 mmol) was dissolved in a mixture of glacial acetic acid (125 mL) and 33% HBr in acetic acid (3.4 mL) and treated with a 0.99 M solution of bromine in acetic acid (73 mL, 72 mmol) at room temperature for 3 hours. The solution was diluted with dichloromethane, washed successively with water, and 10% aq. $NaHSO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the desired bromoketone intermediate which was crystallized from a mixture of dichloromethane and isooctane (14.3 g, 57%): mp 90-93°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.95 (d, J=9.1Hz, 2H), 7.42 (d, J=8.5Hz, 2H), 7.22 (d, J=8.5Hz, 2H), 6.92 (d, J=9.1Hz, 2H), 6.33 (s, 1H), 3.85 (s, 3H), 2.46 (s, 3H). Mass spectrum: M+H = 352.

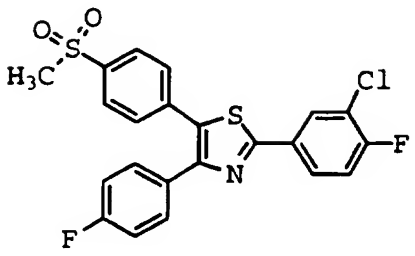
Step 4: Preparation of 2-(2-chlorophenyl)-4-(4-methoxyphenyl)-5-(4-methylthiophenyl)thiazole:

A mixture of the bromoketone intermediate from Step 3 (3.22 g, 9.17 mmol) and 2-chlorothiobenzamide (1.65 g, 9.62 mmol) in acetonitrile (40 mL) was stirred at room temperature for 24 hours. During this time a solid precipitated from solution which was isolated by filtration and air dried to give the desired thiazole (3.26 g, 84%): mp 159-161°C . ^{1}H NMR ($CDCl_3$) 300 MHz 8.38 (m, 1H), 7.54 (d, J=8.9Hz, 2H) 7.48 (d, 1H), 7.33 (m, 4H), 7.22 (d, J=8.5Hz, 2H), 6.88 (d, J=8.9Hz, 2H), 3.82 (s, 3H), 2.51 (s, 3H). Mass spectrum: M+H = 424.

Step 5: Preparation of 2-(2-chlorophenyl)-4-(4-methoxyphenyl)-5-(4-methylsulfonylphenyl)thiazole:

A dichloromethane (5 mL) solution of the thiazole from Step 4 (0.30 g, 0.7 mmol) was treated with MCPBA (0.53 g, 1.5 mmol) and stirred at room temperature for 24 hours. The solution was successively washed with 10% aq. $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid that was crystallized from a mixture of dichloromethane and isooctane to afford pure product (190 mg, 59%): mp 171.5-173.5°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.39 (m, 1H), 7.88 (d, J=8.5Hz, 2H) 7.63 (d, J=8.3Hz, 2H), 7.49 (m, 3H), 7.38 (m, 2H), 6.90 (d, J=8.9Hz, 2H), 3.83 (s, 3H), 3.09 (s, 3H). High resolution mass spectrum Calc'd for $C_{23}H_{18}ClNO_3S_2$: 455.0417. Found: 455.0416. Mass spectrum: M+H = 455.0461.

Example 12



2-(3-Chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

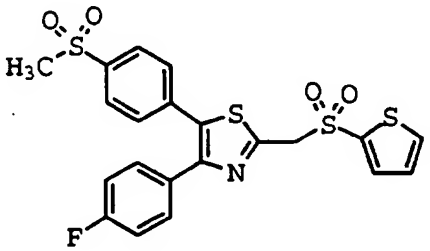
A solution of the intermediate from Example 1 Step 3, 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromoethanone, (1.96 g, 5.78 mmol) and 3-fluoro-4-chlorothiobenzamide (1.14 g, 6.01 mmol) in 15 mL of acetonitrile was heated to reflux for 16 hours. The solution was cooled to room temperature, poured into 50 mL of methanol and chilled in an ice bath whereupon the desired product precipitated. The crude thiazole was recrystallized from methanol to provide the desired thiazole (1.44 g, 58%): mp 113-118°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.10 (dd, J=7.0Hz, 2.2Hz, 1H), 7.85 (m, 1H), 7.57 (m, 2H), 7.26 (m, 5H), 7.02 (t, J=8.5 Hz, 2H), 2.51 (s, 3H). ^{19}F NMR ($CDCl_3$) -112.92 (m), -113.44 (m). Mass spectrum M+H = 429.

Step 2: Preparation of 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A dichloromethane (20 mL) solution of the thiazole from Step 1 (910 mg, 2.12 mmol) was treated with MCPBA (1.48 g, 4.29 mmol) and stirred at room temperature for 30 minutes. The solution was successively washed with 10% aq. $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid that was

crystallized from a mixture of dichloromethane and isooctane to afford pure product (770 mg, 79%): mp 165-167°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.10 (d, 1H), 7.90 (d, J=8.1Hz, 2H), 7.85 (m, 1H), 7.54 (m, 4H), 7.24 (t, 1H), 7.05 (t, J=8.5 Hz, 2H), 3.10 (s, 3H); ^{19}F NMR ($CDCl_3$) -112.06 (m), -112.29 (m). High resolution mass spectrum Calc'd. for $C_{22}H_{14}ClF_2NO_2S_2$: 462.0201. Found: 462.0138.

Example 13



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)sulfonylmethyl)thiazole

Step 1: Preparation of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(2-thienyl)sulfonylmethyl)thiazole:

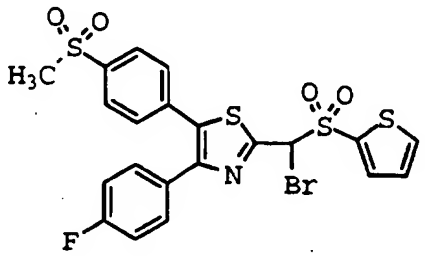
A solution of the intermediate from Example 1 Step 3, 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromoethanone, (4.33 g, 12.76 mmol) and (2-thienyl)sulphonylthioacetamide (2.55 g, 11.5 mmol) in 25 mL of acetonitrile was heated to reflux for 16 hours. The solution was cooled in an ice bath and a precipitate formed that was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, washed successively with sat. aq. $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to provide a brown oil that was purified by flash chromatography on silica gel, eluting with 30% ethyl acetate in hexane. The appropriate fractions were combined and

concentrated and finally recrystallized from a mixture of dichloromethane and isooctane to provide 2.16 g (41%) of pure thiazole: mp 120-121°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.74 (d, J= 4.9Hz, 1H), 7.67 (m, 1H), 7.33 (m, 2H), 7.21 (m, 5H), 6.95 (t, J=8.7Hz, 2H), 4.87 (s, 2H), 2.49 (s, 3H); ^{19}F NMR ($CDCl_3$) -113.33 (m). High resolution mass spectrum Calc'd. for $C_{21}H_{16}FNO_2S_4$: 461.0048. Found: 461.0090.

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)sulfonylmethyl)-thiazole:

A dichloromethane (15 mL) solution of the thiazole from Step 1 (1.74 g, 3.8 mmol) was treated with MCPBA (2.68 g, 7.8 mmol) and stirred at room temperature for 1 hour. The solution was successively washed with 10% aq. $NaHSO_3$, and 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow foam. The foam was crystallized from a mixture of dichloromethane and isooctane to afford 1.55 g, (86%) of pure product as a white solid: mp 98-105°C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.91 (d, J= 8.5Hz, 2H), 7.77 (dd, J=4.8Hz 1.4Hz, 1H), 7.68 (dd, J=3.7Hz 1.1Hz, 1H), 7.51 (d, J=8.1Hz, 2H), 7.29 (m, 2H), 7.17 (t, J=4.8Hz, 1H), 6.98 (t, J=8.8Hz, 2H), 4.89 (s, 2H), 3.09 (s, 3H); ^{19}F NMR ($CDCl_3$) -112.13 (m). High resolution mass spectrum Calc'd. for $C_{21}H_{17}FNO_4S_4$ (MH^+): 494.0025. Found: 494.0005.

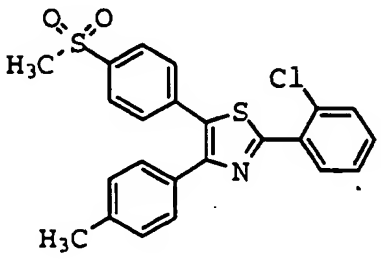
Example 14



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)sulfonylbromomethyl)-thiazol

The product from Example 13 Step 2, [4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)sulfonylmethyl)-thiazole], (0.38 g, 0.76 mmol) was dissolved in chloroform (20 mL). The solution was treated with 0.80 mL of a solution of bromine in acetic acid (0.99 M, 0.78 mmol) and stirred at room temperature for 0.58 hour and was treated with a 10% solution of $NaHSO_3$. The organic layer was collected, washed with saturated $NaHCO_3$, dried over magnesium sulfate and concentrated *in vacuo* to give a white foam (0.46 g) which was a mixture of the brominated compound and starting material. This mixture was purified by flash chromatography on silica gel, eluting with 30% ethyl acetate in hexane to give the product as a white foam (0.20 g, 45%): ^1H NMR ($CDCl_3$) 300 MHz 7.90 (d, J= 8.5Hz, 2H), 7.86 (dd, J=4.8Hz 1.1Hz, 1H), 7.79 (dd, J=3.7Hz 1.1Hz, 1H), 7.55 (d, J=8.5Hz, 2H), 7.31 (m, 2H), 7.21 (t, J=4.7Hz, 1H), 6.98 (t, J=8.8Hz, 2H), 6.24 (s, 2H), 3.09 (s, 3H); ^{19}F NMR ($CDCl_3$) -111.85 (m). Field desorption mass spectrum: M+Li = 579.

Example 15



2-(2-Chlorophenyl)-5-(4-methylsulfonylphenyl)-4-(4-methylphenyl)thiazole

Step 1: Preparation of 3-(4-methylthiophenyl-2-(4-methylphenyl)propenoic acid.

4-Methylthiobenzaldehyde (16.4 mL, 123.7 mmol) was added to 4-methylphenylacetic acid (26.0 g, 173.1 mmol), triethylamine (17.2 mL, 123.7 mmol) and 250 mL of acetic acid. The reaction was warmed to reflux and held at reflux for four hours. Upon cooling to approximately 110°C, water (250 mL) was added over ten minutes, such that foaming was controlled and the reaction temperature remained $\geq$ 90°C. This temperature was maintained for 16 hours, the thick suspension formed was cooled to room temperature and filtered. The solid was washed with water and dried to yield the acid intermediate as orange crystals (32.2 g; 91%): mp 144-160°C. ^{1}H NMR ($CDCl_3$) 300MHz 7.87(s, 1H), 7.41 - 7.02(m, 9H), 2.43 (s, 3H), 2.40 (s, 3H).

Step 2: Preparation of 2-(4-methylthiophenyl)-1-(4-methylphenyl)ethanone:

3-(4-Methylthiophenyl-2-(4-methylphenyl)propenoic acid from Step 1 (25 g, 87.91 mmol) was added to triethylamine (12.9 mL, 92.31 mmol) and toluene (200 mL) and cooled to 0°C. Diphenylphosphoryl azide (19 mL, 87.91 mmol) dissolved in toluene (100 mL), was added to the reaction over approximately ten minutes, keeping the reaction temperature $\leq$ 10°C. After holding the reaction temperature at 0°C for 30 minutes, water (100 mL) was added, and the biphasic solution was extracted with toluene (2x200 mL). The combined organic solution was dried over anhydrous $MgSO_4$ and filtered. Over approximately thirty minutes, the solution was carefully warmed to reflux and held for one hour. Upon removing the heat source, *tert*-butanol (9 mL, 96.7 mmol) was added, and reflux was continued for an additional thirty minutes. Concentrated HCl (8 mL, 96.8 mmol) was added with extreme caution, producing copious evolution of gas. After continuing

reflux for a final twenty minutes, the reaction was cooled to room temperature, and held for 16 hours. The solvent volume was reduced *in vacuo*, until crystals appeared. Diethyl ether (300 mL) was added, and the suspension was cooled to 0°C, held for 30 minutes, filtered and washed with diethyl ether to provide, after air-drying, pure 2-(4-methylthiophenyl)-1-(4-methylphenyl)ethanone (11.3 g, 50%): mp 120-121°C. ^{1}H NMR ($CDCl_3$) 300MHz 7.89(d, J=8.26 Hz, 2H), 7.23 - 7.15(m, 6H), 4.21(s, 2H), 2.45(s, 3H), 2.40(s, 3H).

Step 3: Preparation of 2-bromo-2-(4-methylthiophenyl)-1-(4-methylphenyl)ethanone:

2-(4-Methylthiophenyl)-1-(4-methylphenyl)ethanone from Step 2 (10.0 g, 39.0 mmol) was added to 33% HBr in acetic acid (70 mL) and glacial acetic acid (100 mL). Over approximately 20 minutes, a solution of bromine in acetic acid (1 M, 39 mL) was added to the suspension, and the reaction was held at room temperature for one hour. Any undissolved solids were removed by filtration, and the reaction was concentrated *in vacuo*, to a residue. The residue was dissolved in methylene chloride (100 mL), washed with 5% $Na_2S_2O_5$ (2x100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a colorless oil. The oil was held under vacuum for 16 hours, yielding 2-bromo-2-(4-methylthiophenyl)-1-(4-methylphenyl)ethanone (8.38 g, 64%) as a dirty white solid: mp 97-98°C. ^{1}H NMR ($CDCl_3$) 300MHz 7.86 (d, J = 8.46 Hz, 2H), 7.80(d, J = 8.26 Hz, 2H), 7.33 - 7.16(m, 4H), 5.88(s, 1H), 2.43(s, 3H), 2.36(s, 3H).

Step 4: Preparation of 2-(2-chlorophenyl)-4-(4-methylphenyl)-5-(4-methylthiophenyl)thiazole:

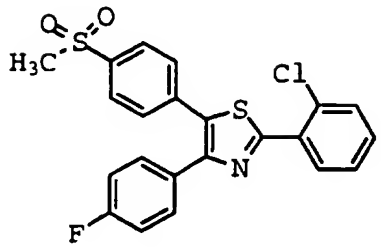
2-Bromo-2-(4-methylthiophenyl)-1(4-methylphenyl)ethanone from Step 3 (0.300 g, 0.895 mmol) was added to acetonitrile (20 mL). 2-Chlorothiobenzamide (0.154 g, 0.895 mmol) was added,

and the suspension was heated and held at reflux for three hours. The reaction was cooled to room temperature, diluted with ethyl acetate (50 mL) and poured into water(50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2x30 mL). The combined organic solution was dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified via flash chromatography (silica gel; 5% ethyl acetate in hexane) to yield 2-(2-chlorophenyl)-4-(4-methylphenyl)-5-(4-methylthiophenyl)thiazole (0.284 g, 78%) as a white solid: mp 125-126°C. ^1H NMR ($CDCl_3$) 300MHz 8.40(m, 1H), 7.62 - 7.11(m, 11H), 2.50 (s, 3H), 3.36(s, 3H). Mass spectrum: MH^+ = 407.

Step 5: Preparation of 2-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)-4-(4-methylphenyl)thiazole:

2-(2-Chlorophenyl)-4-(4-methylphenyl)-5-(4-methylthiophenyl)thiazole from Step 4 (0.243 g, 0.596 mmol) was added to aqueous ethanol (25 mL). Oxone® (1.10 g, 1.787 mmol) was added, and the suspension was stirred at room temperature for 16 hours. Water (25 mL) was added, and the product precipitated. The suspension was cooled to 0°C and held for one hour. The product was filtered, washed with water (25 mL), and dried to yield 2-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)-4-(4-methylphenyl)thiazole (0.236 g, 90%) as a white solid: mp 185-187 °C. ^1H NMR ($CDCl_3$) 300MHz 8.40(m, 1H), 7.89(d, J = 8.26 Hz, 2H), 7.61(d, J = 8.46 Hz, 2H), 7.54 - 7.37(m, 5H), 7.16(d, J = 7.85 Hz, 2H), 3.09(s, 3H), 2.38(s, 3H). Mass spectrum: MH^+ = 439.

Example 16



2-(2-Chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

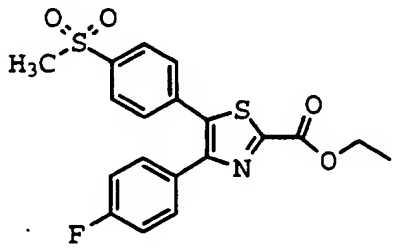
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (2.03 g, 5.98 mmol)(Example 1, Step 3) in acetonitrile (60 mL) in a 125 mL round bottom flask was added 2-chlorothiobenzamide (1.08 g, 6.28 mmol) and the suspension was heated to 80°C for 4 hours. The reaction was cooled to room temperature and the suspension was filtered. The solid was recrystallized from hot acetonitrile (50 mL) and methanol (150 mL) yielding 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole as a tan solid (1.23 g, 50 %): mp 133-134°C. ^{1}H NMR ($CDCl_3$) 300 mHz δ 8.37 (d, J = 6.17 Hz, 1H), 7.60 (dd, J = 8.68, 5.28, 2H) 7.51 (d, J = 9.44 Hz, 1H), 7.32-7.42 (m, 2H), 7.32 (d, J = 8.68 Hz, 2H), 7.21 (d, J = 8.68 Hz, 2H), 7.02 (t, J = 8.68, 2H), 2.51 (s, 3H). MS (EI): m/z 412 (MH^+).

Step 2: Preparation of 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

To a solution of 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole from Step 1 (1.30 g, 3.16 mmol) in methylene chloride (30 mL) at room temperature was added MCPBA (2.03 g, 67% peroxide content, 7.89 mmol) in two portions (T = 0 hour and 1

hour). After stirring for 6 hours, the hazy reaction mixture was diluted with methylene chloride (50 mL) and the resulting clear yellow solution was washed successively with $NaHSO_3$ solution (0.1 M, 3 X 20 mL), $NaHCO_3$ saturated solution (3 X 50 mL), and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (1.2 g, 86 %) as a yellow solid: mp 133-134°C. ^1H NMR ($CDCl_3$) 400 mHz δ 8.42-8.38 (m, 1H), 7.92 (d, J = 8.40 Hz, 2H), 7.61 (d, J = 8.40 Hz, 2H), 7.56-7.45 (m, 3H), 7.38 (m, 2H), 7.05 (t, J = 8.69 Hz, 2H), 3.10 (s, 3H). MS (EI-thermospray): m/z 443 (M+H). HRMS Δ = -2.5 mmu.

Example 17



Ethyl [4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]carboxylate

Step 1: Synthesis of ethyl [4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-thiazolyl]carboxylate:

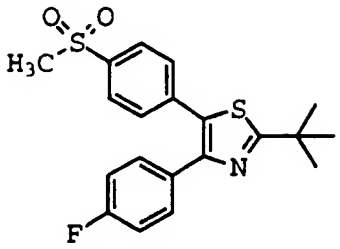
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (1.014 g, 2.99 mmol) (Example 1, Step 3) in ethanol (30 mL) was added ethyl thiooxamate (0.428 g, 3.21 mmol) and the suspension was heated to reflux for 12 hours. The reaction was cooled to room temperature and let stand for 2 days. The crude reaction mixture was concentrated *in vacuo*, diluted with methylene chloride, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified

by flash chromatography (9:1 hexane:ethyl acetate) and recrystallized from methylene chloride and isooctane yielding the ethyl [4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-thiazolyl]carboxylate as a pale yellow solid (0.352 g, 32 %): mp 115-116°C. ^{1}H NMR ($CDCl_3$) 400 mHz δ 7.54-7.48 (m, 2H), 7.25-7.20 (m, 4H), 7.00 (t, J = 8.56 Hz, 2H), 4.50 (q, J= 7.00 Hz, 2H), 2.50 (s, 3H). 1.46 (t, J = 7.09 Hz, 3H). MS (EI): m/z 373 (M^+). HRMS Δ = 0.000 mmu.

Step 2: Preparation of ethyl [4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]carboxylate:

To a solution of ethyl [4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]carboxylate from Step 1 (0.203 g, 0.544 mmol) in methylene chloride (10 mL) was added at 0°C MCPBA (0.294 g of 67 % peroxide content MCPBA, 1.14 mmol). The reaction was warmed to room temperature and let stand for 3 days. The crude reaction mixture was diluted with methylene chloride (50 mL) and the resulting solution was washed successively with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution and brine. The solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding a white foam. This foam was crystallized from methylene chloride and isooctane to yield ethyl [4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]carboxylate as pale yellow small needles (0.150 g, 69 %): mp 173-174°C. ^{1}H NMR ($CDCl_3$) 400 mHz δ 7.93 (d, J = 8.30 Hz, 2 H), 7.55 (d, J = 8.30 Hz, 2H), 7.48 (t, J = 8.79 Hz, 2H), 7.03 (t, J = 8.79 Hz, 2H), 4.52 (q, J = 7.32 Hz, 2H), 3.09 (s, 3H), 1.46 (t, J = 7.33 Hz, 3H). MS (EI): m/z 405 (M^+). HRMS Δ = -0.5 mmu.

Example 18



2-(*tert*-Butyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1 Preparation of 2,2-dimethylthiopropionamide:

To a solution of 2,2-dimethylpropionamide (2.00 g, 19.77 mmol) in toluene (60 mL) was added Lawesson's reagent (4.00 g, 9.89 mmol) and the solution was heated to reflux for 12 hours. The crude reaction mixture was cooled to room temperature and was concentrated *in vacuo*. The crude product was purified by flash chromatography. The first column utilized 3:1 hexane:ethyl acetate yielding a white solid having a strong sulfurous aroma. This solid was further purified by flash chromatography (1:1 methylene chloride:hexane with 1 % acetic acid). The eluant, which contained the desired thioamide, was diluted with toluene and concentrated *in vacuo* yielding an oil. Treatment of this oil with isooctane yielded 2,2-dimethylthiopropionamide (0.190 g, 8%) as a white powder which was used immediately: ^{1}H NMR ($CDCl_3$) 300 mHz δ 9.40 (br s, 1H), 8.65 (br s, 1H), 1.19 (s, 9H).

Step 2: Preparation of 2-(tert-butyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

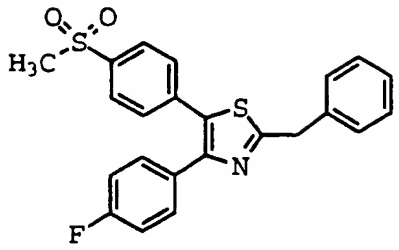
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3) (0.196 g, 0.578 mmol) in ethanol (6 mL) was added 2,2-dimethylthiopropionamide from Step 1 (0.071 g, 0.606

mmol) and the mixture was heated to reflux overnight. The reaction was cooled to room temperature and diluted with ethyl acetate (50 mL). This solution was washed successively with Na_2CO_3 (10% solution) and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole as a pale yellow oil (0.162 g, 78%): ^1H NMR ($CDCl_3$) 300 mHz δ 7.56-7.51 (m, 2H), 7.24 (d, J = 8.48 Hz, 2H), 7.20 (d, J = 8.48 Hz, 2H), 6.98 (t, J = 8.85 Hz, 2H), 2.49 (s, 3H), 1.52 (s, 9H). MS (EI): m/e 357 (M+). HRMS Δ = 0.1 mmu.

Step 3: Preparation of 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

To a solution of 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole from Step 2 (0.110 g, 0.31 mmol) in methylene chloride (5 mL) at 0°C was added MCPBA (67 % peroxide content MCPBA) (0.080 g, 0.62 mmol initially) and the reaction was warmed to room temperature. Additional MCPBA was added (0.020 g, 0.15 mmol) later that day, more (0.040 g, 0.31 mmol) on day 4, and more (0.020 g, 0.15 mmol) later on day 4. The crude reaction mixture was diluted with methylene chloride (50 mL) and the resulting solution was washed successively with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was recrystallized from methylene chloride and isooctane yielding 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole as a white powder (0.059 g, 49 %): mp 144-145°C. ^1H NMR ($CDCl_3$) 400mHz δ 7.87 (d, J = 8.30 Hz, 2H), 7.51-7.45 (m, 4H), 7.00 (t, J = 8.79, 2H), 3.08 (s, 3H), 1.50 (s, 9H). MS (EI): m/z 390 (MH^+). HRMS Δ = 1.9 mmu.

Example 19



2-Benzyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-benzyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

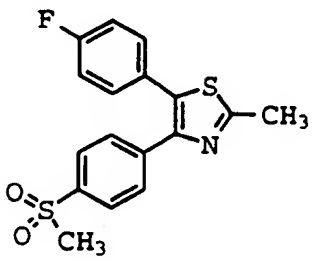
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3) (0.250 g, 0.737 mmol) in ethanol (9 mL) was added 2-phenylthioacetamide (0.111 g, 0.737 mmol) and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, diluted with ethyl acetate (50 mL), washed successively with Na_2CO_3 (10 % solution) and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding an oil. This oil was dissolved in methylene chloride and isooctane yielding a suspension. The solid was removed by filtration and the filtrate reconcentrated *in vacuo* yielding 2-benzyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole as a yellow oil which was suitable based upon ^1H NMR to be used without further purification.

Step 2: Preparation of 2-benzyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

To a solution of 2-(benzyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole from Step 1 (0.20 g, 0.50 mmol) in methylene chloride (10 mL) was added, at room temperature, MCPBA (0.29 g of 67% peroxide content MCPBA, 1.00 mmol) and the reaction was warmed to room

temperature and let stand for 2 hours. The crude reaction mixture was diluted with methylene chloride (50 mL) and the resulting solution was washed successively with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution, and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding a solid. This solid was recrystallized from methylene chloride and isooctane yielding 2-benzyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole as white needles (0.130 g, 56 %): mp 117-118°C. ^1H NMR ($CDCl_3$) 400 mHz δ 7.83 (d, J = 8.56 Hz, 2H), 7.5-7.3 (m, 9H), 7.02 (t, 8.67 Hz, 2H), 4.38 (s, 2H), 3.06 (s, 3H). MS (FAB): m/z 424 (MH+).

Example 20



5-(4-Fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole

Step 1: Preparation of 1-(4-methylthiophenyl)-2-(4-fluorophenyl)ethanone:

To a stirred solution of thioanisole (380 mL, 3.2 mol) and 4-fluorophenylacetyl chloride (300 g, 1.6 mol) in carbon disulfide (1.2 L), cooled to 5°C, was added anhydrous aluminum chloride portionwise at such a rate that the internal temperature did not rise above 15°C. The reaction was stirred at room temperature for 16 hours. The solution was cautiously poured into 2 L of ice and water. The aqueous solution was extracted with methylene chloride (6x150 mL), the combined extracts were dried over anhydrous

$MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in 800 mL of ether and cooled to 0°C whereupon crystals of pure product formed which were isolated by filtration and air dried to provide the ketone (199.6 g, 48%): mp 135-138°C. ^1H NMR ($CDCl_3$/TMS) 300 MHz 8.00 (d, J=8.7 Hz, 2H), 7.40-7.30 (m, 4H), 7.13-7.03 (m, 2H), 4.34 (s, 2H), 2.56 (s, 3H). Mass spectrum M^+=260.

Step 2: Preparation of 2-bromo-2-(4-fluorophenyl)-1-(4-methylthiophenyl)ethanone:

To a stirred slurry of 2-(4-fluorophenyl)-1-(4-methylthiophenyl)ethanone from Step 1 (5.04 g, 19.36 mmol) in acetic acid (100 mL) was added HBr in acetic acid (45 mL, 48 % by wt.) and bromine (1.0 mL, 3.09 g, 19.36 mmol). The resulting green slurry became homogeneous within 30 minutes. After 4 hours, the reaction was concentrated *in vacuo*, the residue diluted with toluene, and reconcentrated *in vacuo*. The crude haloketone was purified by flash chromatography (2:1 hexane:methylene chloride) and recrystallized from ethyl acetate and isooctane yielding 2-bromo-2-(4-fluorophenyl)-1-(4-methylthiophenyl)ethanone as an off-white solid (4.51 g, 69 %): mp 108-111 °C. ^1H NMR ($CDCl_3$) 300 mHz δ 7.94 (d, J = 8.79 Hz, 2H), 7.60 - 7.50 (m, 2H), 7.25 (d, J = 8.79 Hz, 2H), 7.10 (t, J = 8.67 Hz, 2H), 6.34 (s, 1H), 2.56 (s, 3 H).

Step 3: Preparation of 5-(4-fluorophenyl)-4-(4-methylthiophenyl)-2-methylthiazole:

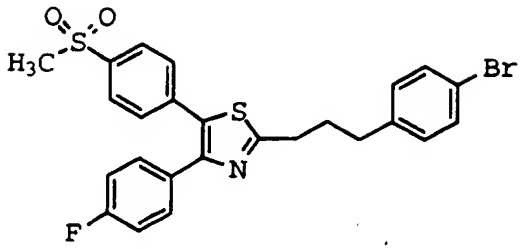
To a solution of 2-bromo-2-(4-fluorophenyl)-1-(4-methylthiophenyl)ethanone from Step 2 (0.70 g, 2.10 mmol) in ethanol (20 mL) was added thioacetamide (0.16 g, 2.10 mmol) and the mixture was heated to reflux for 20 hours. The reaction was cooled to room temperature and concentrated *in vacuo* and dissolved in methylene chloride. This solution was washed with $NaHCO_3$

saturated solution and dried over Na_2SO_4, filtered and reconcentrated *in vacuo* yielding a white crystalline solid. Flash chromatography of this solid (2:1 methylene chloride:hexane) yielded 5-(4-fluorophenyl)-4-(4-methylthiophenyl)-2-methylthiazole as a white solid (0.45 g, 68 %): mp 104-105°C. ^1H NMR ($CDCl_3$) 400 mHz δ 7.39 (d, J = 8.32, 2H), 7.28 (dd, J = 8.80, 5.14, 2H), 7.15 (d, J = 8.32, 2H), 7.00 (t, J = 8.80, 2H), 2.74 (s, 3H), 2.47 (s, 3H). MS (EI): m/z 316 (M+H). HRMS Δ = 0.000 mmu.

Step 4: Preparation of 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole:

To a solution of 2-(methyl)-5-(4-fluorophenyl)-4-(4-methylthiophenyl)thiazole from Step 3 (0.440 g, 1.39 mmol) in methylene chloride (15 mL) at 0°C was added MCPBA (0.90 g of 67% peroxide content MCPBA, 3.49 mmol) and the reaction was warmed to room temperature and let stand overnight. The crude reaction mixture was diluted with methylene chloride (70 mL) and the resulting solution was washed successively with $NaHSO_3$ solution (0.1 M) and $NaHCO_3$ saturated solution, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:1 methylene chloride:hexane) and the product thus obtained was recrystallized from methylene chloride and isooctane yielding 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole as clear colorless needles (0.274 g, 57%): mp 134-135°C. ^1H NMR ($CDCl_3$) 400 mHz δ 7.84 (d, J = 8.56 Hz, 2H), 7.69 (d, J = 8.56 Hz, 2H), 7.28 (m, 2H), 7.06 (t, J = 8.68, 2H), 3.04 (s, 3H), 2.76 (s, 3H). MS (EI): m/z 348 (MH+); HRMS Δ = -2.5 mmu.

Example 21



2-(3-[4-Bromophenyl]propyl)-4-(4-fluorophenyl))-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 4-(4-bromophenyl) thiobutyramide:

To a solution of 4-(4-bromophenyl)butyramide (1.653 g, 6.827 mmol) in toluene (35 mL) was added Lawesson's reagent (1.381 g, 3.414 mmol). The reaction was heated at reflux overnight, cooled to room temperature, and concentrated yielding an orange oil. Flash chromatography of this oil (1:1 hexane:methylene chloride with 1% acetic acid) yielded 4-(4-bromophenyl) thiobutyramide as off-white needles (0.196 g): mp 104-105°C. ^{1}H NMR (DMSO-d_6) 300 MHz δ 9.33 (br s, 1H), 9.12 (br s, 1H), 7.44 (d, J = 8.11 Hz, 2H), 7.14 (d, J = 8.48 H z, 2H), 2.56-2.41 (m, 4H), 1.95 - 1.85 (m , 2H).

Step 2: Preparation of 2-(3-[4-bromophenyl]propyl)-4-(4-fluorophenyl))-5-(4-methylthiophenyl)thiazole:

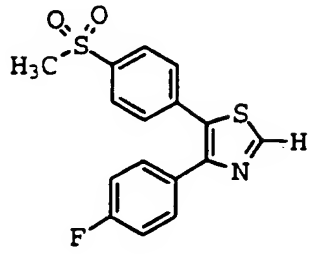
To a solution of 2-bromo-2-(4-fluorophenyl)-1-(4-methylthiophenyl)ethanone (Example 1, Step 3) (2.70 g, 7.90 mmol) in acetonitrile (90 mL) and ethanol (10 mL) was added 4-(4-bromophenyl) thiobutyramide from Step 1, (1.4 g, 7.90 mmol) and the mixture was heated to reflux for 7 hours. The reaction was cooled to room temperature and let stand overnight. The crude product was concentrated *in vacuo* yielding an oil which was

purified by flash chromatography (1:1 hexane:methylene chloride) yielding 2-(3-[4-bromophenyl]propyl)-4-(4-fluorophenyl))-5-(4-methylthiophenyl)thiazole (1.4 g, 36 %) as a clear colorless oil (ca. 90 % purity by ^1H NMR): ^1H NMR ($CDCl_3$) 300 MHz δ 7.50-7.46 (m, 2H), 7.41 (d, J = 8.46 Hz, 2H), 7.22 (d, J = 8.66 Hz, 2H), 7.16 (d, J = 8.66 Hz, 2H), 7.10 (d, J = 8.26 Hz, 2H), 6.97 (t, J = 8.86, 2H), 3.03 (t, J = 7.45 Hz, 2H), 2.74 (t, J = 7.45 Hz, 2H), 2.49 (s, 3H), 2.20 - 2.09 (m, 2H). MS (EI): m/z 529, 531 (M+) 497, 499. HRMS Δ = -2.1 mmu.

Step 3 Preparation of 2-(3-[4-bromophenyl]propyl)-4-(4-fluorophenyl))-5-(4-methylsulfonylphenyl)thiazole:

To a solution of 2-(3-[4-bromophenyl]propyl)-4-(4-fluorophenyl))-5-(4-methythiophenyl)thiazole from Step 2 (0.20 g, 0.48 mmol) in methylene chloride (5 mL) at 0°C was added MCPBA (0.17 g of 67% peroxide reagent, 0.65 mmol) and the solution was warmed to room temperature and let stand overnight. The reaction mixture was diluted with methylene chloride (50 mL), was washed successively with $NaHSO_3$ solution (0.1 M), and $NaHCO_3$ saturated solution, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was recrystallized from methylene chloride and isooctane yielding 2-(3-[4-bromophenyl]propyl)-4-(4-fluorophenyl))-5-(4-methylsulfonylphenyl)thiazole as a white crystalline solid (0.113 g, 44%): mp 132-133°C. ^1H NMR ($CDCl_3$) 300 MHz δ 7.86 (d, J = 8.46 Hz, 2H), 7.49 - 7.40 (m, 6H), 7.11 - 7.08 (m, 2H), 7.01 (t, J = 8.66 Hz, 2H), 3.08 - 3.03 (m, 5H), 2.75 (t, J = 7.45 Hz, 2H), 2.18 (m, 2H). MS (EI): m/z 529,5311 (M+). HRMS Δ = -3.117 mmu.

Example 22



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 4-(4-fluorophenyl))-5-(4-methylthiophenyl)thiazole:

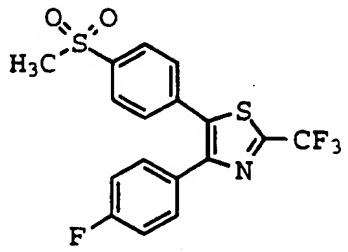
To a solution of formamide (3.4 g, 3.0 mL, 75.5 mmol) in diethyl ether was added, with ice bath cooling and stirring solid, phosphorous pentasulfide (2.35 g, 5.3 mmol) in several portions. The reaction was refrigerated at 5°C for 72 hours, warmed to room temperature and stirred for an additional 16 hours. The ethereal solution of resulting thioformamide was decanted from the reaction mixture and used "as is". One half of this ethereal solution was concentrated *in vacuo* The resulting straw colored oil was diluted with acetonitrile (10 mL) and cooled to 0°C (ice bath). Solid 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3) (0.518 g, 1.53 mmol) was added and the reaction was stirred at room temperature for 8 days. The reaction mixture was concentrated *in vacuo*, diluted with methylene chloride and washed successively with $NaHCO_3$ saturated solution, and brine, dried over Na_2SO_4, filtered and reconcentrated *in vacuo*. The crude thiazole was purified by flash chromatography (1:1 hexane:methylene chloride) yielding 4-(4-fluorophenyl))-5-(4-methylthiophenyl)thiazole as a clear viscous oil (0.37 g, 80%): ^1H NMR ($CDCl_3$) 300 MHz δ 8.75 (s, 1H), 7.52

(dd, J = 8.87, 5.47 Hz, 2H), 7.22 (d, J = 8.68, 2H), 7.17 (d, J = 8.68, 2H), 6.98 (t, J = 8.87 Hz, 2H), 2.45 (s, 3H). MS (EI): m/e 301 (M+). HRMS Δ = 5.063 mmu.

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

To a solution of 4-(4-fluorophenyl))-5-(4-methylthiophenyl)thiazole from Step 1 (0.35 g, 1.16 mmol) in methylene chloride (12 mL) at 0°C was added MCPBA (0.75 g of 67% peroxide content reagent, 2.90 mmol). The solution was warmed to room temperature and stirred overnight. The reaction was diluted with methylene chloride (40 mL) and this solution was successively washed with $NaHSO_3$ solution (0.1 M), and $NaHCO_3$ saturated solution, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was recrystallized from methylene chloride and isooctane yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole as long pale yellow needles (0.253 g, 65%): mp 138-139°C. ^1H NMR ($CDCl_3$) 300 MHz δ 8.89 (s, 1H), 7.91 (d, J = 8.68, 2H), 7.55 (d, J = 8.68, 2H), 7.48 (dd, J = 9.06, 5.28Hz, 2H), 7.03 (t, J = 9.06 Hz, 2 H), 3.09 (s, 3H). MS (EI): m/z 333 (M+). HRMS Δ = -5.342 mmu.

Example 23



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazol

Step 1: Preparation of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-trifluoromethylthiazole:

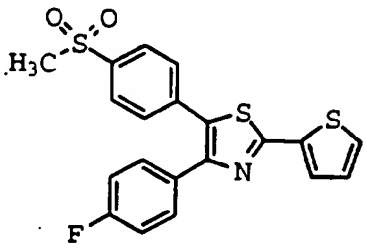
To a solution of trifluoroacetamide (13.7 g, 121.2 mmol) in toluene (30 mL) was added solid phosphorous pentasulfide (5.4 g, 12.1 mmol) and the mixture was heated to reflux for 60 hours. The resulting orange "coarse" suspension was cooled to room temperature and pulverized to form a fine suspension. 2-Bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3) (1.53 g, 4.50 mmol) was added in one portion to the toluene suspension (7.5 mL, ca. 30 mmol of theory). This suspension was heated to reflux for 1.5 hours, cooled to 50°C, and 1.0 N HCl solution (1 mL) was added carefully. The solution was reheated to reflux for 1 hour more. This reaction was cooled to room temperature and let stand overnight. To this solution was added 2 N NaOH solution until the exotherm subsided and the reaction was stirred for 1 hour longer. The resulting black suspension was diluted with methylene chloride and washed with $NaHCO_3$ saturated solution, dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding an orange oily semi-solid. This crude intermediate was purified by flash chromatography with 3:1 hexane:ethyl acetate and 9:1 hexane:methylene chloride yielding 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-trifluoromethylthiazole (1.1 g, 72%) as a pale brown oil: ^1H NMR ($CDCl_3$) 300 MHz δ 7.52 (dd, J = 5.28, 9.06, 2H), 7.24 (m, 4H), 7.01 (t, J = 8.68 Hz, 2H), 2.51 (s, 3H). MS (EI): m/z 369 (M+H). HRMS Δ = -1.446 mmu.

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole:

To a solution of 2-trifluoromethyl-5-(4-fluorophenyl))-4-(4-methylthiophenyl)thiazole from Step 1 (1.10 g, 3.30 mmol) in methylene chloride (30

mL) at 0°C was added MCPBA (2.10 g of 67% peroxide content reagent, 8.20 mmol) in three portions over 2 hours. After 3 hours total reaction time, the reaction was diluted with methylene chloride (150 mL) and the solution was washed with $NaHSO_3$ solution (0.1 M):$NaHCO_3$ saturated solution (1:1 ration 3x50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was recrystallized from methylene chloride and isooctane yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole as opaque white crystals (1.1 g, 90%): mp 168-170°C. ^1H NMR ($CDCl_3$) 300 MHz δ 7.97 (d, J = 8.84, 2H), 7.57 (d, J = 8.84, J = 8.84, 2H), 7.47 (dd, J = 8.85, J = 5.16, 2H), 7.04 (t, J = 8.85 Hz, 2H), 3.11 (s, 3H); ^{19}F NMR ($CDCl_3$) 300 MHz δ -61.55, -111.42. MS (EI): m/z 402 (MH^+). HRMS Δ = 1.938 mmu.

Example 24



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole

Step 1: Preparation of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(2-thienyl)thiazole:

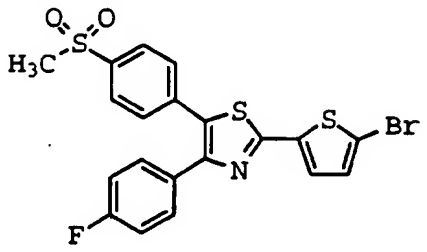
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3) (0.249 g, 0.734 mmol) in ethanol (9 mL) was added thiophene-2-thiocarboxamide (0.110 g, 0.771 mmol) and the mixture was heated to reflux 14 hours. The reaction was cooled to room temperature, diluted with ethyl acetate (50 mL) and this solution washed successively

with Na_2CO_3 (10 % solution, 3x20 mL) and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding an orange crystalline solid. This solid was purified by flash chromatography (9:1 hexane:ethyl acetate) yielding 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(2-thienyl]thiazole (0.228 g, 82%) as a viscous yellow oil: ^1H NMR ($CDCl_3$) 300 MHz δ 7.53-7.58 (m, 3H), 7.40 (dd, J = 5.29, 1.17 Hz, 1H), 7.28 (d, J = 8.30 Hz, 2H), 7.19 (d, J = 8.30 Hz, 2H), 7.09 (dd, J = 4.91, 3.78 Hz, 1H), 7.00 (t, J = 8.68 Hz, 2H), 2.50 (s, 3H). MS (EI): m/e 383 (M^+). HRMS Δ = 0.1 mmu.

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole:

To a solution of 2-(2-thienyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole from Step 1 (0.20 g, 0.52 mmol) in methylene chloride (5 mL), MCPBA was added at 0°C (0.27 g of 67 % peroxide content MCPBA, 1.1 mmol) and the reaction was warmed to room temperature. The crude reaction mixture was diluted with methylene chloride (50 mL) and the resulting solution was washed successively with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was recrystallized from methylene chloride and isooctane yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole as a pale green solid (0.170 g, 79%): mp 194-195°C. ^1H NMR (DMSO-d_6) 400 MHz δ 7.90 (d, J = 8.30 Hz, 2H), 7.58 (d, J = 3.91 Hz, 1H), 7.55-7.50 (m, 4H), 7.45 (d, J = 3.91 Hz, 1H), 7.13-7.11 (m, 1H), 7.04 (t, J = 8.79 Hz, 2H), 3.09 (s, 3H). MS (EI): m/z 416 (MH^+). HRMS Δ = 0.9 mmu.

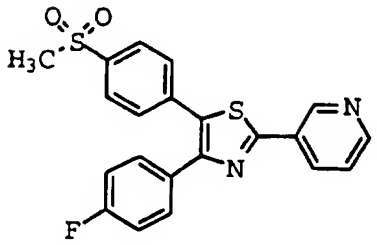
Example 25



2-(5-Bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

To a solution of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(2-thienyl]thiazole (Example 24, Step 1) (0.057 g, 0.149 mmol) suspended in acetic acid (2 mL) and methylene chloride (2.0 mL) was added excess bromine in acetic acid (1.4 M, 0.51 mL, 0.714 mmol). The reaction was concentrated *in vacuo*, diluted with ethyl acetate, and washed successively with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution and brine, dried over Na_2SO_4, filtered and reconcentrated *in vacuo*. The resulting compound was diluted with methylene chloride (1 mL) and MCPBA (0.064 g of 67% peroxide reagent, 2.48 mmol) and let stand for 4 hours. The crude reaction mixture was diluted with methylene chloride (50 mL) and the resulting solution was washed successively with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution and brine, dried over Na_2SO_4, filtered and again concentrated *in vacuo*. The crude product was recrystallized from methylene chloride and isooctane yielding 2-(5-bromo-2-thienyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-thiazole as fine yellow needles (0.039 g, 53 %): mp 190-191°C. ^1H NMR ($CDCl_3$) 300 MHz δ 7.89 (d, J = 8.46 Hz, 2H), 7.54 (d, J = 8.46 Hz, 2H), 7.49 (m, 2H), 7.30 (d, J = 4.03 Hz, 1H), 7.08 (m 1H), 7.04 (t, J = 8.66 Hz, 2H), 3.09 (s, 3H). MS (EI): m/z 496 (M+H).

Example 26



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(3-pyridyl)thiazole

Step 1: Preparation of 1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone:

To a stirred solution of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3) (15.00 g, 57.62 mmol) in methylene chloride (500 mL) at 5°C (ice-bath) was added MCPBA (29.64 g, ca. 67% peroxide, ca. 113 mmol), portionwise over 30 minutes. The solution was warmed to room temperature. The reaction solution was stirred vigorously with $NaHSO_3$ solution for 10 minutes to quench any unreacted MCPBA. The layers were separated and ethyl acetate was added to aid in dissolution of the precipitate which began to form. The partial suspension was filtered and the solid saved. The organic phase was washed successively with $NaHCO_3$ solution and brine, dried over Na_2SO_4, and diluted with isooctane until a solid began to precipitate. More solid precipitated upon removal of most of the solvent *in vacuo*. All of the precipitates were combined yielding 1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (14.5 g, 86 %). mp 182-183°C. ^1H NMR ($CDCl_3$) 300 MHz δ 8.04 (dd, J = 5.24, 8.46, 2H), 7.92 (d, J = 8.26 Hz, 2H), 7.46 (d, J = 8.46 Hz, 2H), 7.17 (t, J = 8.46, 2H), 4.37 (s, 2H), 3.05 (s, 3H). MS: m/z 293 (MH+); HRMS Δ = 1.6 mmu.

Step 2: Preparation of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone:

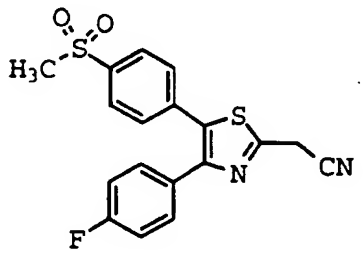
To a stirred slurry of 1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone from Step 1 (3.03 g, 10.38 mmol) in acetic acid (40 mL) was added HBr in acetic acid (2 mL, 48% by wt.) and bromine (0.64 mL, 1.99 g, 12.45 mmol). Within minutes the slurry became homogeneous. After 1 hour, the reaction was concentrated *in vacuo*, diluted with methylene chloride and reconcentrated *in vacuo* yielding 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone as a tan solid (3.53 g, 95 %) which could be used without further purification: mp 140-141°C, ^{1}H NMR ($CDCl_3$) 300 MHz δ 8.05 (dd, J = 5.16, 8.84 Hz, 2H), 7.96 (d, J = 8.48 Hz, 2H), 7.75 (d, J = 8.48 Hz, 2H), 7.17 (t, J = 8.48 Hz, 2H), 6.29 (s, 1H), 3.06 (s, 3H). MS: m/e 371/373 (MH^+). HRMS Δ = 5.5 mmu.

Step 3: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(3-pyridyl)thiazole:

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone from Step 2 (0.732 g, 1.97 mmol) in acetonitrile (20 mL) was added thionicotinamide (0.273 g, 1.97 mmol) with stirring. The resulting solution was heated to reflux for 1 hour and additional 2-bromo-1-(4-fluorophenyl)-3-(methylsulfonylphenyl)ethanone (0.031 g, 0.05 mmol) was added and stirred at reflux for an additional hour. The reaction was cooled to room temperature and concentrated *in vacuo* yielding an orange semi-solid. This was purified by flash chromatography (2:1 hexane:ethyl acetate with 1% acetic acid). The product fractions were combined, toluene added, and the resulting solution reconcentrated *in vacuo* yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(3-pyridyl)thiazole as a pale yellow crystalline solid

(0.351 g, 43%): mp 143-146°C. ^{1}H NMR ($CDCl_3$) 400 MHz δ 9.20 (d, J = 1.81 Hz, 1H), 8.68 (dd, J = 1.46, 4.89 Hz, 1H), 8.30 (dt, J = 2.00, 9.42 Hz, 1H), 7.91 (d, J = 8.55 Hz, 2H), 7.60-7.52 (m, 4H), 7.42 (m, 1), 7.05 (t, J = 8.70 Hz, 2H), 3.10 (s, 3H). MS (EI): m/z 410 (M^+). HRMS Δ = -4.3 mmu.

Example 27



2-(Cyanomethyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(cyanomethyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

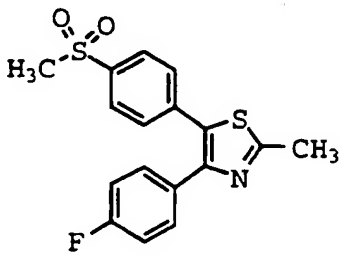
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.249 g, 0.734 mmol) in ethanol (9 mL) was added 2-cyanothioacetamide (0.077 g, 0.771 mmol) and the solution was heated to reflux for 14 hours. The reaction was cooled to room temperature, was concentrated *in vacuo* and the residue was dissolved in ethyl acetate. This solution was washed successively with Na_2CO_3 (10% solution) and brine, dried over Na_2SO_4, filtered and reconcentrated *in vacuo* yielding an orange crystalline solid. The solid was purified by flash chromatography (4:1 hexane:ethyl acetate) yielding 2-(cyanomethyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole as very fine pink crystals (0.090 g, 36%): mp 118-119°C. ^{1}H NMR ($CDCl_3$) 400 MHz δ 7.50 (d, J = 5.38, 2H), 7.47 (d, J = 5.38, 2H), 7.24-7.18 (m, 4H), 7.00 (t, J = 8.80, 2H), 4.16 (s,

2H), 2.50 (s, 3H). MS (EI): m/z 340 (M^+). HRMS Δ = 2.7 mmu.

Step 2: Preparation of 2-(cyanomethyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

To a solution of 2-cyanomethyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole from Step 1 (0.08 g, 0.24 mmol) in methylene chloride (3 mL) at 0°C was added MCPBA (0.13 g of 67 % peroxide content MCPBA, 0.48 mmol) and the reaction was warmed to room temperature. The crude reaction mixture was diluted with methylene chloride (50 mL), washed successively with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution, and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was recrystallized from methylene chloride and isooctane yielding 2-(cyanomethyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole as light orange needles (0.064 g, 72%): mp 151-152°C. ^1H NMR ($CDCl_3$) 400 MHz δ 7.92 (d, J = 8.79, 2H), 7.52 (d, J = 8.79, 2H), 7.44 (m, 2H), 7.03 (t, J = 8.30, 2H), 4.17 (s, 2H), 3.09 (s, 3H). MS (EI): m/z 373 (M+H). HRMS Δ = 4.8 mmu.

Example 28

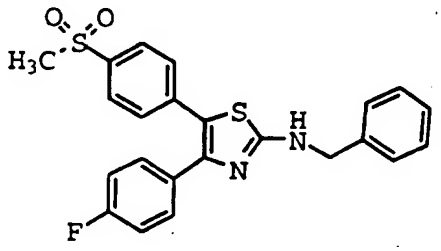


4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-methylthiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (0.437 g, 1.18 mmol)

(Example 26, Step 2) in acetonitrile (10 mL) was added thioacetamide (0.088 g, 1.18 mmol) and the solution was heated to reflux (2 hours) until all solid dissolved. The reaction was cooled to room temperature. The acetonitrile was removed *in vacuo* and the resulting product precipitated from methanol by the addition of water yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-methylthiazole (0.226 g, 55 %, ca. 85% purity by ^{1}H NMR): mp 229-233°C. ^{1}H NMR ($CDCl_3$) 300 MHz δ 7.98 (d, J = 8.11 Hz, 2H), 7.66-7.61 (m, 2H), 7.52 (d, J = 8.48 Hz, 2H), 7.13 (t, J = 8.48 Hz, 2H), 3.31 (s, 1H), 3.10 (s, 3H). MS (EI-thermospray): m/z 348 (M+). HRMS Δ = -2.3 mmu.

Example 29

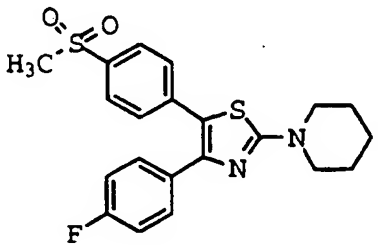


4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.415 g, 1.12 mmol) in isopropanol (12 mL) was added N-benzyl thiourea (0.186 g, 1.12 mmol). The solution was heated to reflux (30 hours), cooled to room temperature and let stand for 7 days. The resulting suspension was concentrated *in vacuo*. The resulting residue was suspended in methylene chloride (100 mL) and washed with $NaHCO_3$ saturated solution (3x10 mL), dried over sodium sulfate, filtered and reconcentrated *in vacuo* yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole as a pale

yellow solid (0.34 g, 69%): mp 112°C. ^{1}H NMR ($CDCl_3$) 400 MHz δ 7.74 (d, J = 8.56 Hz, 2H), 7.43-7.25 (m, 10H), 6.92 (t, J = 8.56 Hz, 2H), 4.33 (s, 2H), 3.02 (s, 3H). MS (EI-thermospray): m/z 439 (MH+). HRMS Δ = 1.6 mmu.

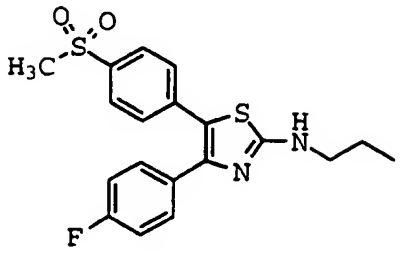
Example 30



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-piperidinyl)thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (0.462 g, 1.24 mmol) (Example 26, Step 2) in ethanol (10 mL) was added piperidine thiocarboxamide (0.198 g, 1.37 mmol) and the solution was heated to reflux for 14 hours. The reaction was cooled to room temperature and concentrated *in vacuo* yielding a foam. This foam was dissolved in methylene chloride and washed successively with $NaHCO_3$ saturated solution (3 portions) and brine, dried over Na_2SO_4, filtered and reconcentrated *in vacuo* yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-piperidinyl)-thiazole (0.371 g, 72%) as a yellow-green fluffy solid: mp 173-175°C, ^{1}H NMR ($CDCl_3$) 400 MHz δ 7.77 (d, J = 8.56 Hz, 2H), 7.46 (dd, J = 5.60, 8.80), 7.38 (d, J = 8.56 Hz, 2H), 6.99 (t, J = 8.80 Hz, 2H), 3.53 (s (broad), 4H), 3.05 (s, 3H), 1.70 (s (broad), 6H). MS (EI): m/z 417 (MH+). HRMS Δ = -1.5 mmu.

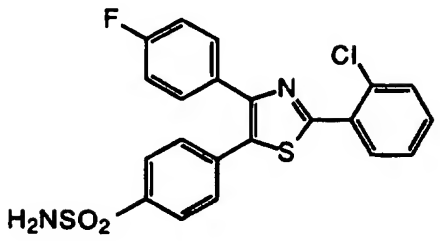
Example 31



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (0.346 g, 0.932 mmol) (Example 26, Step 2) in ethanol (15 mL) was added N-propylthiourea (0.116 g, 0.979 mmol) with stirring. The resulting solution was heated to reflux for 24 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in methylene chloride, washed successively with Na_2CO_3 (10 % solution) and brine, dried over Na_2SO_4, filtered and reconcentrated *in vacuo* yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole as a yellow crystalline solid (0.276 g, 76 %): mp 181-182°C. ^1H NMR (DMSO-d_6) 400 MHz δ 7.97 (t, J = 5.37 Hz, 1H), 7.78 (d, J = 8.79 Hz, 2H), 7.42 (dd, J = 5.86, 8.79, 2H), 7.37 (d, J = 8.79, 2H), 7.15 (t, J = 8.79 Hz, 2H), 3.21 (q, J = 6.84, 2H), 3.18 (s, 3H), 1.60 (m, 2H), 0.91 (t, J = 7.33, 3H). MS (EI): m/z 390 (M+). HRMS Δ = 2.4 mmu.

Example 32

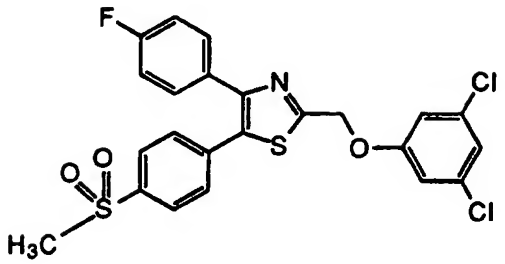


I

4-[4-(4-Fluorophenyl)-2-(2-chlorophenyl)-5-thiazolyl]benzenesulfonamide

To a solution of the methyl sulfone (Example 16) (0.21 g, 0.47 mmol) in tetrahydrofuran (THF) (5 mL) at 0°C under nitrogen was added 2 M n-butyl magnesium chloride in THF (1.0 mL, 2.0 mmol) slowly, via syringe, and the mixture was stirred at 0°C for 30 minutes and then at room temperature (25°C) for 2 hours. After cooling to 0°C, a 1.0 M solution of triethyl borane in THF (2.5 mL, 2.5 mmol) was added and the mixture was warmed to room temperature and stirred for 2 hours, and then heated to reflux overnight (18 hours). After cooling to room temperature for 3 hours, water (3 mL) was added followed by sodium acetate (1.2 g) and hydroxylamine-O-sulfonic acid (0.82 g). After stirring at room temperature overnight, the mixture was poured into 3 volumes of ethyl acetate, and the organic layer washed with water and brine and dried over $MgSO_4$. After solvent removal, the white solids (a mixture of product and starting material) was recrystallized from ethyl acetate/hexane to provide 0.11 g of a white solid. Anal. Calc'd for $C_{21}H_{14}N_2O_2S_2FCl$: C, 56.69; H, 3.17; N, 6.30. Found: C, 55.99; H, 2.97; N, 6.15.

Example 33



2-[(3,5-Dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole

Step 1: Preparation of 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

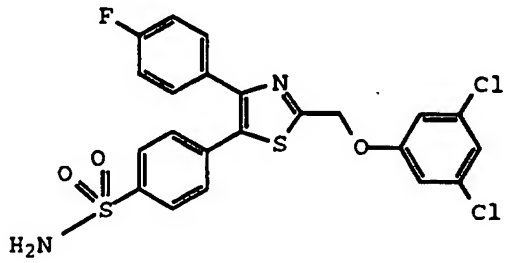
A solution of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromoethanone, (Example 1, Step 3) (4.01 g, 11.8 mmol) and 3,5-dichlorophenoxy thioacetamide (2.80 g, 11.9 mmol) in 20 mL of acetonitrile and 10 mL of ethanol was heated to reflux for 1.2 hours. The solution was diluted with methanol, cooled to 0°C in an ice bath and a precipitate formed that was removed by filtration to provide pure 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-((3,5-dichlorophenoxy)methyl)thiazole (4.19 g; 74%) which was used directly in the next step: mp 104.5-105.0°C; Mass spectrum M+H=476.

Step 2: Preparation of 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A dichloromethane (30 mL) solution of the thiazole from Step 1 (4.06 g, 8.52 mmol) was treated with *m*-chloroperoxybenzoic acid (5.98 g, 17.06 mmol) and stirred at room temperature for 0.75 hour. The

solution was washed successively with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid. Recrystallization from a mixture of dichloromethane and isooctane afforded 2.50 g (58%) of pure 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole as a white solid: mp 171-173°C; ^1H NMR ($CDCl_3$) 300 MHz 7.88 (d, J= 8.5Hz, 2H), 7.54 (d, J= 8.5Hz, 2H), 7.50-7.40 (m, 2H), 7.07-6.90 (m, 5H), 5.37 (s, 2H), 3.08 (s, 3H); ^{19}F NMR ($CDCl_3$) 112.53 (m). High resolution mass spectrum Calc'd. for $C_{23}H_{16}ClFNO_3S_2$ (MH^+): 506.9933. Found: 506.9932.

Example 34

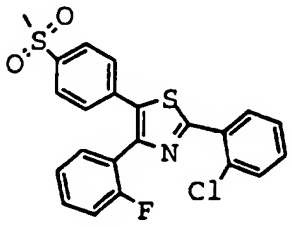


4-[2-((3,5-Dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-thiazolyl]benzenesulfonamide

To a solution of 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (Example 33) (0.508 g, 1.0 mmol) in THF (5 mL) at 0°C under nitrogen was added 2.0 M n-butyl magnesium chloride in THF (1.6 mL, 3.2 mmol) slowly, via syringe, and the mixture stirred at 0°C for 30 minutes and then at room temperature (25°C) for 2 hours. After cooling to 0°C, a 1.0 M solution of triethyl borane in THF (5 mL, 5 mmol) was added and the mixture was warmed to room temperature and stirred for 2 hours, and then heated to reflux for 36 hours. After cooling

to room temperature and stirring for 3 hours, water (3 mL) was added followed by sodium acetate (1.2 g) and hydroxylamine-O-sulfonic acid (0.82 g). After stirring at room temperature overnight, the mixture was poured into 3 volumes of ethyl acetate, and the organic layer washed with water and brine and dried over $MgSO_4$. After solvent removal, the white solids (a mixture of product and starting material) were purified by flash chromatography on silica gel using 30% ethyl acetate/70% hexane to provide 4-[4-(4-fluorophenyl)-2-((3,5-dichlorophenoxy)methyl)-5-thiazolyl]benzenesulfonamide as a white solid (0.147 g): Anal. Calc'd for $C_{22}H_{15}N_2O_3S_2FCl_2$: C, 51.87; H, 2.97; N, 5.50. Found: C, 52.19; H, 2.84; N, 5.40 .

Example 35



2-(2-Chlorophenyl)-4-(2-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-(2-fluorophenyl)-3-(4-methylthiophenyl)propenoic acid:

Acetic anhydride (60 mL), 4-(methylthio)benzaldehyde (7.05 g, 44 mmol), 2-fluorophenylacetic acid (7.79 g, 50.5 mmol), and triethylamine (5.50 g, 54.5 mmol) were heated to reflux for 1.75 hours. The reaction was cooled to 90°C, and water (100 mL) was added cautiously. This caused the solution to reflux vigorously and the temperature to rise to 135°C. A yellow precipitate formed and after cooling to room temperature the solid

was collected by filtration, washed with water, and recrystallized from toluene to provide 2-(2-fluorophenyl)-3-(4-methylthiophenyl)propenoic acid as yellow needles (7.98 g, 63%): mp 151.5-156.0°C. ^1H NMR ($CDCl_3$) 300 MHz 8.01 (s, 1H), 7.41-7.00 (m, 8H), 2.43 (s, 3H). ^{19}F NMR ($CDCl_3$) -113.40 (m). Mass spectrum $M+H^+$=289.

Step 2: Preparation of 1-(2-fluorophenyl)-2-(4-methylthiophenyl)ethanone:

A solution of 2-(2-fluorophenyl)-3-(4-methylthiophenyl)propenoic acid from Step 1 (7.86 g, 27.3 mmol) and triethylamine (2.80 g, 27.7 mmol) in 22 mL of anhydrous toluene was cooled to 0°C and treated with diphenylphosphoryl azide (7.73 g, 28.1 mmol). The solution was stirred at 0°C for 20 minutes and at room temperature for 3.50 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to reflux and a vigorous evolution of gas occurred. After 0.75 hours, 11 mL of *tert*-butyl alcohol was added to the reaction. After an additional twenty minutes, concentrated hydrochloric acid (5 mL) was added slowly and the reaction was heated at 90 °C overnight (14 hours). The solution was cooled to room temperature and diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to provide a brown solid that was purified by crystallization from ether to afford 1-(2-fluorophenyl)-2-(4-methylthiophenyl)ethanone as a yellow solid (4.60 g, 65%): mp 58-59.5°C. ^1H NMR ($CDCl_3$) 300 MHz 7.84 (m, 1H), 7.52 (m, 1H), 7.23-7.08 (m, 6H), 4.25 (d, J=2.6Hz, 2H), 2.46 (s, 3H). ^{19}F NMR ($CDCl_3$) -108.51 (m). Mass spectrum $M+H^+$=261.

Step 3: Preparation of 1-(2-fluorophenyl)-2-(4-methylthiophenyl)-2-bromo-ethanone:

1-(2-Fluorophenyl)-2-(4-methylthiophenyl)ethanone from Step 2 (4.36 g, 16.7 mmol) was added to acetic acid (30 mL) and 33% HBr in acetic acid (0.5 mL). The solution was stirred and treated with bromine (17 mL, 16.8 mmol, 1.0 M in acetic acid) from the addition funnel at such a rate that the bromine color was discharged rapidly, ca. 15 min. After an additional 50 minutes at room temperature, the solution was concentrated *in vacuo* to give a brown oil. The crude haloketone was dissolved in dichloromethane and washed with 1N $NaHSO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give 1-(2-fluorophenyl)-2-(4-methylthiophenyl)-2-bromo-ethanone as an oil that solidified upon standing (4.83 g, 85%): mp 58-63°C. ^1H NMR ($CDCl_3$) 300 MHz 7.87 (td, J=7.6, 1.8Hz, 1H), 7.52 (m, 1H), 7.39 (d, J=8.3Hz, 2H), 7.27-7.03 (m, 4H), 6.34 (s, 1H), 2.45 (s, 3H). ^{19}F NMR ($CDCl_3$) -108.51 (m). Mass spectrum M^+=338.

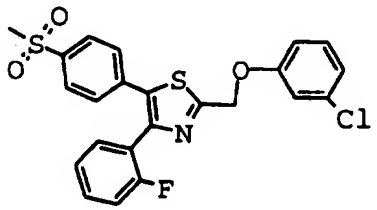
Step 4: Preparation of 2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

A solution of 1-(2-fluorophenyl)-2-(4-methylthiophenyl)-2-bromo-ethanone from Step 3 (1.39 g, 4.1 mmol) and 2-chlorothiobenzamide (0.71 g, 4.1 mmol) in 10 mL of ethanol was heated to reflux for 4.4 hours. The solution was cooled to room temperature and poured into 25 mL of methanol, and chilled with an ice bath whereupon crystals of pure product formed which were isolated by filtration and air dried to afford the thiazole (1.34 g, 79%): mp 117-119°C. ^1H NMR ($CDCl_3$) 300 MHz 8.37 (m, 1H), 7.62 (m, 2H), 7.49 (d, J=7.7Hz,1H), 7.32 (m, 7H), 7.22 (d, J=8.5Hz, 2H), 2.51 (s, 3H). Mass spectrum M^++H =412.

Step 5: Preparation of 2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A solution of 2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(4-methylthiophenyl)thiazole (1.12 g, 2.72 mmol) in 20 mL of dichloromethane was treated with m-chloroperoxybenzoic acid (1.91 g, 5.53 mmol) at 0°C for 20 minutes. The solution was washed with 10% aqueous $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid that was purified by recrystallization from a mixture of dichloromethane and isooctane to provide 660 mg (55%) of pure product: mp 163-166°C. ^1H NMR ($CDCl_3$) 300 MHz 8.37 (m, 1H), 7.86 (d, J=8.5Hz, 2H), 7.63 (td, J=7.7, 1.8Hz, 2 H), 7.53 (d, J=8.5Hz, 2H), 7.53 (m, 1H), 7.38 (m, 3H), 7.26 (t, J=7.4Hz, 1H), 7.05 (t, J=9.6Hz, 1H), 3.06 (s, 3H). ^{19}F NMR ($CDCl_3$) -113.33 (m). High resolution mass spectrum Calc'd. for $C_{22}H_{15}ClFNO_2S_2$: 443.0217. Found: 443.0176.

Example 36



2-(3-Chlorophenoxy)methyl-4-(2-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole

Step 1: Preparation of 2-((3-chlorophenoxy)methyl)-4-(2-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

A solution of 1-(2-fluorophenyl)-2-(4-methylthiophenyl)-2-bromo ethanone, (1.64 g, 4.8 mmol) (Example 34, Step 3) and 3-chlorophenoxy thioacetamide (0.98 g, 4.8 mmol) in 25 mL of acetonitrile was heated

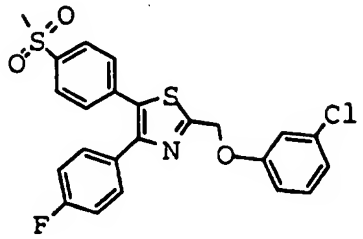
to reflux for 14 hours. The solution was diluted with methanol, cooled to 0°C in an ice bath and a precipitate formed that was removed by filtration to provide pure 2-((3-chlorophenoxy)methyl)-4-(2-fluorophenyl)-5-(4-methylthiophenyl)thiazole (0.69 g; 32%). The filtrate was concentrated *in vacuo*, and the residue dissolved in ethyl acetate, washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to provide additional product that was crystallized from a mixture of dichloromethane and isooctane to provide 200 mg of additional material for a total yield of 890 mg (42%): mp 115-118°C: ^1H NMR ($CDCl_3$) 300 MHz 7.52-6.90 (m, 12H), 5.38 (s, 2H), 2.46 (s, 3H). ^{19}F NMR ($CDCl_3$) -113.61 (m). High resolution mass spectrum Calc'd. for $C_{23}H_{17}ClFNOS_2$ (M^+): 441.0424. Found: 441.0467.

Step 2: Preparation of 2-((3-chlorophenoxy)methyl)-4-(2-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A dichloromethane (5 mL) solution of 2-((3-chlorophenoxy)methyl)-4-(2-fluorophenyl)-5-(4-methylthiophenyl)thiazole from Step 1 (0.85 g, 1.9 mmol) was treated with m-chloroperoxybenzoic acid (1.33 g, 3.9 mmol) and stirred at room temperature for 15 hours. The solution was washed with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid that was recrystallized from a mixture of dichloromethane and isooctane to afford 0.71 g (78%) of pure 4-(2-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-((3-chlorophenoxy)methyl)thiazole as a white solid: mp 151.5-153°C. ^1H NMR ($CDCl_3$) 300 MHz 7.84 (d, J=8.3Hz, 2H), 7.50 (m, 1H), 7.46 (d, J=8.3Hz, 2H), 7.39 (m, 1H), 7.24 (m, 2H), 7.06 (m, 3H), 6.92 (m, 1H), 5.41 (s, 2H), 3.06 (s, 3H). ^{19}F NMR ($CDCl_3$) -113.64 (m). High resolution mass spectrum Calc'd.

for $C_{23}H_{17}ClFNO_3S_2$ (MH^+): 473.0322. Found: 473.0346.

Example 37



2-((3-Chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-((3-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

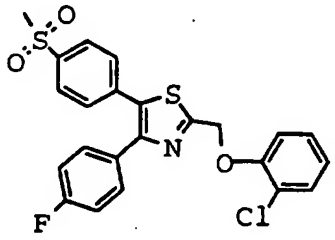
A solution of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromo-ethanone (1.98 g, 5.84 mmol) (Example 1, Step 3) and 3-chlorophenoxy thioacetamide (1.18 g, 5.85 mmol) in 15 mL of acetonitrile and 10 mL of ethanol was heated to reflux for 16 hours. The solution was diluted with methanol, cooled to 0°C in an ice bath and a precipitate formed that was removed by filtration. The solid was air dried and recrystallized from methanol to provide (1.67 g; 65%),of pure 2-((3-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole: mp 106-110°C, ^1H NMR ($CDCl_3$) 300 MHz 7.50 (m, 2H), 7.30-7.15 (m, 5H), 7.09-6.87 (m, 5H), 5.38 (s, 2H), 2.50 (s, 3H). ^{19}F NMR ($CDCl_3$) -113.58 (m). Mass spectrum M^+= 441.

Step 2: Preparation of 2-((3-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A dichloromethane (10 mL) solution of 2-((3-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole (0.65 g, 1.47 mmol) was

treated with m-chloroperoxybenzoic acid (1.03 g, 2.98 mmol) and stirred at room temperature for 1.2 hours. The solution was washed with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid that was recrystallized from dichloromethane to afford 0.50 g (72%) of pure 2-((3-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole as a white solid: mp 128.5-131°C ^1H NMR ($CDCl_3$) 300 MHz 7.89 (d, J=8.1 Hz, 2H), 7.52 (d, J=8.1Hz, 2H), 7.46 (m, 1H), 7.25 (t, J=8.5Hz, 1H), 7.03 (m, 3H), 6.95 (m, 1H), 5.39 (s, 2H), 3.08 (s, 3H). ^{19}F NMR ($CDCl_3$) -112.43 (m). Mass spectrum M+H+= 474.

Example 38



2-((2-Chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-((2-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

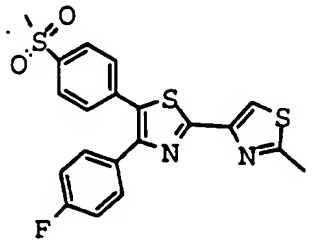
A solution of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromo-ethanone (2.05 g, 6.04 mmol) (Example 1, Step 3) and 2-chlorophenoxy thioacetamide (1.21 g, 6.0 mmol) in 30 mL of acetonitrile was heated to reflux for 3 hours. The solution was diluted with methanol, cooled to 0°C in an ice bath and a precipitate formed that was removed by filtration. The crude solid was further purified by flash chromatography over silica gel and the appropriate fractions were combined, concentrated *in vacuo* and

crystallized from methanol to provide 2.60 g (98%) of pure 4-2-((2-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole: mp 126-129°C, ^{1}H NMR ($CDCl_3$) 300 MHz 7.55-7.39 (m, 4H), 7.28-6.90 (m, 8H), 5.44 (s, 2H), 2.49 (s, 3H). ^{19}F NMR ($CDCl_3$) -114.00 (m). Mass spectrum M+H$^+$= 442.

Step 2: Preparation of 2-((2-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A dichloromethane (50 mL) solution of 2-((2-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole from Step 1 (2.65 g, 6.0 mmol) was treated with m-chloroperoxybenzoic acid (4.19 g, 12.1 mmol) and stirred at room temperature for 3 hours. The solution was washed with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid that was purified by flash chromatography (silica gel) eluting with hexane/ethyl acetate to afford 2.08 g (73%) of pure 2-((2-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole as a white solid, after concentration of the appropriate fractions: mp 189-191°C ^{1}H NMR ($CDCl_3$) 300 MHz 7.89 (d, J=8.5 Hz, 2H), 7.53 (d, J=8.5Hz, 2H), 7.50-7.47 (m, 3H), 7.23 (m, 1H), 7.10-6.95 (m, 4H), 5.47 (s, 2H), 3.08 (s, 3H). ^{19}F NMR ($CDCl_3$) -112.75 (m). High resolution mass spectrum Calc'd. for $C_{23}H_{17}ClFNO_3S_2$: 473.0322. Found: 473.0374.

Example 39



4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-(2-methyl-4-thiazolyl)thiazole

Step 1: Preparation of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-[2-(methyl)-4-thiazolyl]thiazole:

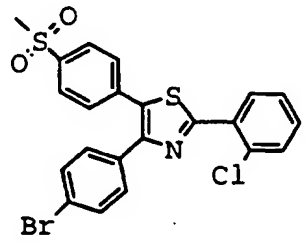
A solution of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromoethanone (9.69 g, 28.6 mmol) (Example 1, Step 3) and 2-methylthiazole-4-thiocarboxamide (3.90 g, 24.7 mmol) in 35 mL of acetonitrile and 20 mL of ethanol was heated to reflux for 1 hour. The solution was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. The crude solid was purified by flash chromatography over silica gel eluting with 1:1 hexane:ethyl acetate. The appropriate fractions were combined and the solvent removed *in vacuo* to provide pure 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-[2-(methyl)-4-thiazolyl]thiazole (4.79 g; 49%): mp 132.5-135°C. ^1H NMR ($CDCl_3$) 300 MHz 7.89 (s, 1H), 7.55 (m, 2H), 7.25 (d, J=8.5Hz, 2H), 7.17 (d, J=8.5Hz, 2H), 7.01 (t, J=8.8Hz, 2H), 2.78 (s, 3H), 2.49 (s, 3H). ^{19}F NMR ($CDCl_3$) -113.80 (m). Mass spectrum $M+H^+$= 399.

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-[2-(methyl)-4-thiazolyl]thiazole:

A dichloromethane (15 mL) solution of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-[2-(methyl)-4-thiazolyl]thiazole from Step 1 (0.71 g, 1.78 mmol) was treated with m-chloroperoxybenzoic acid (1.25 g, 3.62 mmol) and stirred at room temperature for 2 hours. The solution was washed with 10% aq. $NaHSO_3$, 10%

Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid that was purified by crystallization from a mixture of dichloromethane and isooctane to afford pure 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-[2-(methyl)thiazol-4-yl]thiazole (0.37 g, 48%) as a white solid: mp 184-185.5°C. ^1H NMR ($CDCl_3$) 300 MHz 7.93 (s, 1H), 7.88 (d, J=8.5Hz, 2H), 7.54 (d, J=8.5Hz, 2H), 7.53 (m, 2H), 7.04 (t, J=8.8Hz, 2H), 3.08 (s, 3H), 2.79 (s, 3H). ^{19}F NMR ($CDCl_3$) -112.61 (m). Mass spectrum M^+= 430.

Example 40



4-(4-Bromophenyl)-2-(2-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole

Step 1: Preparation of 2-(4-bromophenyl)3-(4-methylthiophenyl)propenoic acid:

A mixture of acetic anhydride (100 mL), 4-(methylthio)benzaldehyde (12.61 g, 82.8 mmol), 4-bromophenylacetic acid (17.79 g, 82.7 mmol), and triethylamine (8.48 g, 83.8 mmol) was heated to reflux for 4.25 hours. The reaction was cooled to 90°C, and water (100 mL) was added. A yellow solid separated from the solution and was isolated by filtration and air dried and recrystallized from a mixture of ethyl acetate and isooctane to afford the acid (12.83 g, 44%): mp 187-190°C. ^1H NMR (acetone d^6) 300 MHz 7.83 (s, 1H), 7.57 (d, J=8.5Hz, 1H), 7.20 (d, J=8.5Hz, 2H),

7.10 (d, J=8.1Hz, 2H), 7.08 (d, J=8.1Hz, 1H), 2.46 (s, 3H). Mass spectrum M^++H=350.

Step 2: Preparation of 1-(4-bromophenyl)2-(4-methylthiophenyl)ethanone:

A solution of 3-(4-methylthiophenyl)-2-(4-bromophenyl)propenoic acid from Step 1 (12.66 g, 36 mmol) and triethylamine (4.27 g, 42 mmol) was dissolved in 60 mL of anhydrous toluene, cooled to 0°C and treated with diphenylphosphoryl azide (10.04 g, 36 mmol). The solution was maintained at 0°C for 0.5 hour and warmed to room temperature for 3.33 hours. The reaction was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo* to remove the ether. The remaining toluene solution was heated to 100 °C for 1 hour. *tert*-Butyl alcohol (6.5 mL) was added to the reaction mixture. After an additional ten minutes, concentrated hydrochloric acid (4 mL) was cautiously added and the reaction maintained at 80°C for 72 hours. After cooling with an ice bath, a solid separated and was isolated by filtration, washed with water, and air dried to afford pure white ketone (8.41 g, 72%): mp 158.5-163°C. ^{1}H NMR (acetone d^6) 300 MHz 8.00 (d, J=8.3Hz, 2H), 7.71 (d, J=8.3Hz, 2H), 7.24 (s, 4H), 4.35 (s, 2H), 2.47 (s, 3H). Mass spectrum M^++H= 321 and 323.

Step 3: Preparation of 2-bromo-1-(4-bromophenyl)-2-(4-methylthiophenyl)ethanone:

A solution of 1-(4-bromophenyl)-2-(4-methylthiophenyl)ethanone from Step 2 (8.40 g, 26 mmol) in acetic acid (135 mL) and 33% HBr in acetic acid (1.5 mL) was treated with a 0.99 M solution of bromine in acetic acid (27 mL, 26.6 mmol) and stirred at room temperature for ten minutes. The solution was concentrated *in vacuo* and the residue taken up in

dichloromethane, washed with 1N $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a gray solid which was recrystallized from a mixture of dichloromethane and isooctane to provide the bromoketone (8.50 g, 81%): mp 107-111°C. ^1H NMR ($CDCl_3$) 300 MHz 7.83 (d, J=8.7Hz, 2H), 7.58 (d, J=8.7Hz, 2H), 7.41 (d, J=8.3Hz, 2H), 7.22 (d, J=8.3Hz, 2H), 6.27 (s, 1H), 2.47 (s, 3H). Mass spectrum M^++H=399, 401 and 403.

Step 4: Preparation of 4-(4-bromophenyl)-2-(2-chlorophenyl)-5-(4-methylthiophenyl)thiazole:

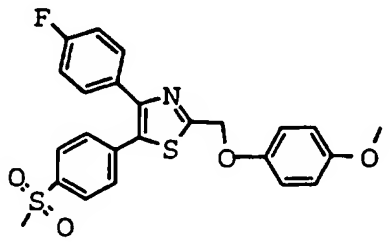
A solution of 2-bromo-1-(4-bromophenyl)-2-(4-methylthiophenyl)ethanone from Step 3 (1.18 g, 2.9 mmol) and 4-chlorothiobenzamide (520 mg, 3.0 mmol) in 40 mL of acetonitrile was heated to reflux for 1.75 hours. The solution was cooled to room temperature, poured into 100 mL of methanol and chilled with an ice bath, whereupon white crystals of pure product formed which were isolated by filtration and air dried. The product was further purified by flash chromatography over silica gel eluting with 8% ether in hexane to afford pure thiazole (1.10 g, 79%) which was used directly in the next step: mp 133-135°C, ^1H NMR ($CDCl_3$) 300 MHz 8.35 (m, 1H), 7.52-7.21 (m, 11H), 2.51 (s, 3H). Mass spectrum M^++H=474.

Step 5: Preparation of 4-(4-bromophenyl)-2-(2-chlorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

A solution of 4-(4-bromophenyl)-2-(2-chlorophenyl)-5-(4-methylthiophenyl)thiazole from Step 4 (1.06 g, 2.2 mmol) in 15 mL of dichloromethane was treated with m-chloroperoxybenzoic acid (1.60 g, 4.6 mmol) at room temperature for 0.08 hour. The solution was diluted with additional dichloromethane, washed with 10% aq. $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a

white solid that was purified by recrystallization from a mixture of dichloromethane and isooctane to give the product (850 mg, 75%): mp 168-184°C. ^{1}H NMR ($CDCl_3$) 300 MHz 8.38 (m, 1H), 7.92 (d, J=8.5Hz, 2H), 7.60 (d, J=8.5Hz, 2H), 7.54-7.38 (m, 7H), 3.10 (s, 3H). High resolution mass spectrum Calc'd. for $C_{22}H_{15}BrClNO_2S$: 502.9416. Found: 502.9436.

Example 41



4-(4-Fluorophenyl)-2-[(4-methoxyphenoxy)methyl]-5-[4-(methylsulfonyl)phenyl]thiazole

Step 1: Preparation of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-((4-methoxyphenoxy)methyl)thiazole:

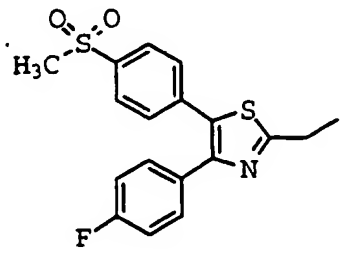
A solution of 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-2-bromo-ethanone, (Example 1, Step 3) (2.30 g, 6.8 mmol) and 4-methoxyphenoxy thioacetamide (1.35 g, 6.8 mmol) in 20 mL of acetonitrile was heated to reflux for 1.1 hours. The solution was concentrated *in vacuo* and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a solid that was recrystallized from a mixture of ethyl acetate and isooctane to provide pure 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-((4-methoxyphenoxy)methyl)thiazole (1.60 g; 54%): mp 89-92°C, ^{1}H NMR ($CDCl_3$) 300 MHz

7.47 (dd, J= 3.2, 8.7Hz, 2H), 7.23 (d, J= 8.5Hz, 2H), 7.17 (d, J=8.5Hz, 2H), 6.98 (m, 4H), 6.86 (d, J=9.1Hz, 2H), 5.33 (s, 2H), 3.78 (s, 3H), 2.49 (s, 3H). ^{19}F NMR ($CDCl_3$) -114.07 (m). Mass spectrum $M+H^+$= 438.

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-((4-methoxyphenoxy)methyl)thiazole:

A dichloromethane (20 mL) solution of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-((4-methoxyphenoxy)methyl)thiazole from Step 1 (1.45 g, 3.3 mmol) was treated with m-chloroperoxybenzoic acid (2.32 g, 6.7 mmol) and stirred at room temperature for 0.42 hour. The solution was washed with 10% aqueous $NaHSO_3$, 10% Na_2CO_3, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a tan solid that was recrystallized from a mixture of dichloromethane and isooctane to afford 0.93 g (60%) of pure 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-((4-methoxyphenoxy)methyl)thiazole as a light tan solid: mp 160-164°C. ^1H NMR ($CDCl_3$) 300 MHz 7.88 (d, J= 8.3Hz, 2H), 7.71 (d, J= 8.3Hz, 2H), 7.45 (dd, J=5.4, 8.7Hz, 2H), 7.03 (d, J=8.7Hz, 5H), 6.98 (d, J=9.1Hz, 2H), 8.68 (d, J=9.1Hz, 2H), 5.35 (s, 2H), 3.77 (s, 3H), 3.08 (s, 3H). ^{19}F NMR ($CDCl_3$) 112.80 (m). High resolution mass spectrum Calc'd. for $C_{24}H_{20}FNO_4S_2$: 469.0818. Found: 469.0854.

Example 42



2-Ethyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

Step 1: Preparation of 2-ethyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

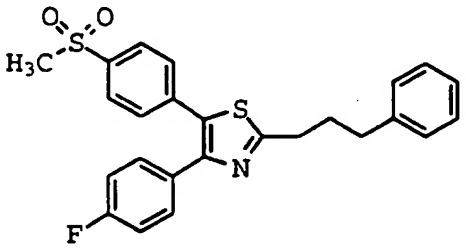
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3) (0.250 g, 0.737 mmol) in ethanol (9 mL) was added thiopropionamide (0.066 g, 0.737 mmol) and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, diluted with ethyl acetate (50 mL), washed with $NaHCO_3$ (10% solution), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude thiazole was recrystallized from methylene chloride and isooctane yielding 2-ethyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole (0.14 g, 57 %) as pale yellow crystals: mp 73-74°C; ^1H NMR ($CDCl_3$) 300 MHz 7.55 (m, 2H), 7.26 (d, J = 7.85, 2H), 7.21 (d, J = 7.85, 2H), 7.03 (t, J = 7.85, 2 H), 3.12 (q, J = 7.50 Hz, 2H), 2.54 (s, 3H), 1.47 (t, J = 7.50 Hz, 3 H); MS (FAB) m/z 330.08 (MH+), HRMS (EI) Δ = -4.2 mmu.

Step 2: Preparation of 2-ethyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

To a solution of 2-ethyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole from step 1 (0.105 g, 0.32 mmol) in methylene chloride (5 mL) was added at room temperature MCPBA (0.21 g of 67% peroxide content MCPBA, 0.80 mmol) and the reaction was warmed to room temperature and stand for 2 hours. The crude reaction mixture was diluted with methylene chloride (50 mL) and the resulting solution was washed with NaHSO3 solution (0.1 M), $NaHCO_3$ saturated solution, and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding a solid. This solid was purified by flash chromatography (hexane:ethyl acetate 1:1 with 2%

acetic acid) yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-ethylthiazole (0.080g, 69%) as a white foam: mp 156-157°C; ^{1}H NMR ($CDCl_3$) 300 MHz 7.86 (d, J = 8.48 Hz, 2H), 7.45 (m, 4 H), 7.00 (t, 8.48 Hz, 2H), 3.13-3.05 (m, 5H), 1.44 (t, J = 7.37 Hz, 3H); MS (FAB) m/z 362.07 (MH+), HRMS (MH+) Δ = -2.6 mmu.

Example 43



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(3-phenylpropyl)thiazole

Step 1: Preparation of 4-phenylthiobutyramide:

To a solution of 4-phenylbutyramide (0.373 g, 2.28 mmol) in toluene (15 mL) was added Lawesson's reagent (0.461 g, 1.14 mmol). The reaction was heated at reflux overnight, cooled to room temperature and concentrated yielding an orange oil. Flash chromatography of this oil (1:1 hexane:methylene chloride with 1% acetic acid) yielded 4-phenylthiobutyramide (0.184 g) as a white solid: ^{1}H NMR (DMSO d_6) 400 MHz 9.33 (s, 1 H), 9.13 (s, 1 H), 7.29-7.23 (m, 2 H), 7.20-7.15 (m, 3 H), 2.56 (t, J = 7.58 Hz, 2 H), 2.50-2.42 (m, 2 H), 2.00-1.85 (m, 2 H).

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(3-phenylpropyl)thiazole:

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, step 3) (0.100 g, 0.295 mmol) in ethanol (3 mL) was added 4-

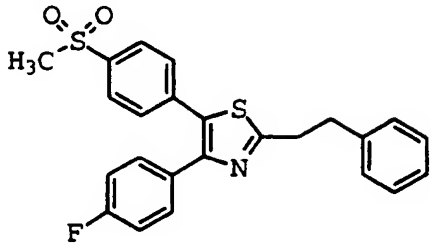
phenylthiobutyramide from step 1 (0.055 g, 0.310 mmol) and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, diluted with ethyl acetate (50 mL), washed with Na_2CO_3 (10% solution), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude thiazole was purified by flash chromatography (9:1, hexane:ethyl acetate) yielding 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(3-phenylpropyl)thiazole (0.118 g, 95%) as crystalline solid: mp 62-63°C; ^1H NMR ($CDCl_3$) 300 MHz 7.49 (d of d, J = 5.52 and 8.85, 2H), 7.33 - 7.14 (m, 9H), 6.98 (t, J = 8.85, 2H), 3.05 (t, J = 7.74, 2 H), 2.82 (t, J = 7.74 Hz, 2H), 2.49 (s, 3H), 2.18 (m, 2 H); MS (FAB) m/z 420 (MH+).

Step 3: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(3-phenylpropyl)thiazole:

To a solution of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(3-phenylpropyl)thiazole from step 2 (0.11 g, 0.26 mmol) in methylene chloride (3 mL) was added at room temperature MCPBA (0.20 g of 67% peroxide content MCPBA, 0.79 mmol) and the reaction was warmed to room temperature and let stand for 2 days. The crude reaction mixture was diluted with methylene chloride (50 mL) and the resulting solution was washed with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution, and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. This product was purified by flash chromatography (1:1 hexane:ethyl acetate with 2% acetic acid) yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(3-phenylpropyl)thiazole (0.040 g, 34 %) as an oily off-white foam: ^1H NMR ($CDCl_3$) 300 MHz 7.87 (d, J = 8.31 Hz, 2H), 7.52 - 7.42 (m, 2 H), 7.38 (d, 8.68 Hz, 2H), 7.76 - 7.18 (m, 5 H), 7.11 (t, J = 8.68 Hz, 2 H), 3.15 (t, J = 7.55 Hz, 2H), 3.05 (s, 3 H), 2.83 (t, J = 7.55

Hz, 2 H), 2.19 (m 2 H); MS (EI) m/z 452.12 (MH+), HRMS (MH+) Δ = -3.1 mmu.

Example 44



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-phenylethyl)thiazole

Step 1: Preparation of 3-phenylthiopropionamide:

To a solution of 3-phenylpropionamide (1.653 g, 6.827 mmol) in toluene (20 mL) was added Lawesson's reagent (0.716 g, 1.77 mmol). The reaction was heated at reflux overnight, cooled to room temperature and concentrated, yielding an orange oil. Flash chromatography of this oil (1:1 hexane:methylene chloride with 1% acetic acid) yielded 3-phenylthiopropionamide (0.070 g) as a white solid: mp 82-83°C; ^{1}H NMR (DMSO d_6) 300 MHz 9.35 (br s, 1 H), 9.15 (br s, 1 H), 7.34-7.10 (m, 2 H), 2.95 (t, J = 8.48 Hz, 2 H), 2.72 (t, J = 8.48 Hz, 2 H).

Step 2: Preparation of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(2-phenylethyl)thiazole

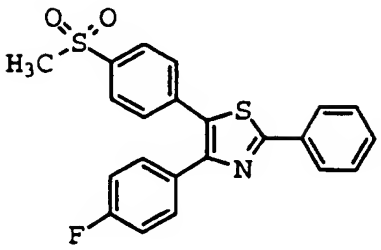
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3)(0.115 g, 0.340 mmol) in ethanol (4 mL) was added 3-phenylthiopropionamide from Step 1 (0.059 g, 0.357 mmol) and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, diluted with ethyl acetate (50 mL), washed with Na_2CO_3 (10 % solution), brine, dried over Na_2SO_4, filtered and

concentrated *in vacuo* yielding 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(2-phenylethyl)thiazole (0.090 g, 65%) as oily crystals: mp 97-99°C; ^{1}H NMR ($CDCl_3$) 300 MHz 7.50 (d of d, J = 5.38 and 8.80, 2 H), 7.35 - 7.15 (m, 9H), 6.99 (t, J = 8.80, 2H), 3.35 (t, J = 8.80, 2 H), 3.19 (t, J = 8.56 Hz, 2H), 2.49 (s, 3H); MS (EI) m/z 405.10 (MH+), HRMS (M+) Δ = 0.0 mmu.

Step 3: Preparation of 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-phenylethyl)thiazole

To a solution of 4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-(2-phenylethyl)thiazole from Step 2 (0.080 g, 0.21 mmol) in methylene chloride (3 mL) was added at room temperature MCPBA (0.110 g of 67% peroxide content MCPBA, 0.42 mmol) and the reaction was warmed to room temperature and let stand for 2 days. The crude reaction mixture was diluted with methylene chloride (50 mL) and the resulting solution was washed with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution, and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. This product was recrystallized from methylene chloride and isooctane yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-phenylethyl)thiazole (0.111g, 100%) as a fluffy white solid: mp 153-154°C; ^{1}H NMR ($CDCl_3$) 400 MHz 7.86 (d, J = 8.30 Hz, 2H), 7.48 - 7.42 (m, 4 H), 7.37 - 7.22 (m, 5 H), 7.02 (t, J = 8.79 Hz, 2 H), , 5 H), 3.39 (t, J = 6.84 Hz, 2H), 3.19 (t, J = 7.32, 2 H), 3.08 (s, 3 H); MS (CI) m/z 438 (MH+), HRMS (MH+) Δ = 2.4 mmu.

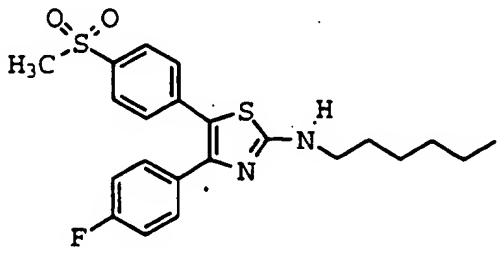
Example 45



4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-phenylthiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.468 g, 1.26 mmol) in acetonitrile (10 mL) was added thiobenzamide (0.164 g, 1.20 mmol) and the solution was heated to reflux (19 hours). The reaction was cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with $NaHCO_3$ saturated solution (3 x 10 mL), dried over sodium sulfate, filtered and concentrated yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-phenylthiazole (0.085 g, 16%) as a fine white powder: mp 188-189°C, ^1H NMR ($CDCl_3$) 300 MHz 8.01 (m, 2H), 7.90 (d, J = 8.48 Hz, 2 H), 7.62-7.55 (m, 4 H), 7.55-7.44 (m, 3 H), 7.04 (t, J = 8.85 Hz, 2 H), 3.09 (s, 3H); MS (EI-thermospray) m/z 410 (MH+). HRMS (EI) Δ = -2.0 mmu.

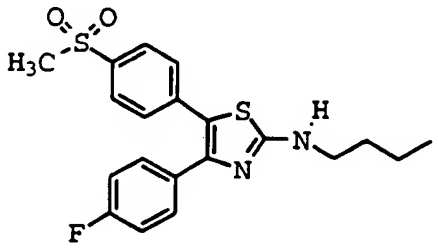
Example 46



4-(4-Fluorophenyl)-2-n-hexylamino-5-(4-methylsulfonylphenyl)thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.503 g, 1.35 mmol) in ethanol (10 mL) was added N-hexylthiourea (0.239, 1.49 mmol). The solution was heated to reflux for 14 hours and was cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with $NaHCO_3$ saturated solution (3 x 10 mL), dried over sodium sulfate, filtered and concentrated yielding 4-(4-fluorophenyl)-2-n-hexylamino-5-(4-methylsulfonylphenyl)thiazole (0.420 g, 72%) as a white powder: mp 161-162°C, ^1H NMR (DMSO d_6) 400 MHz 7.95 (t, J = 5.38 Hz, 1 H), 7.77 (d, J = 8.79 Hz, 2 H), 7.44-7.36 (m, 4 H), 7.15 (t, J = 9.28, 2 H), 3.24 (q , J = 5.86, 2H), 3.18 (s, 3 H), 1.61-1.52 (m, 2 H), 1.38-1.20 (m, 6 H), 0.85 (t, J = 6.84 Hz, 3 H); MS (FAB) m/z 433 (MH+). HRMS Δ = -0.9 mmu.

Example 47

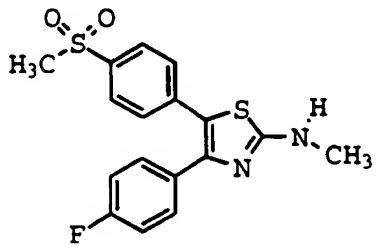


2-Butylamino-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.384 g, 1.03 mmol) in ethanol (15 mL) was added N-butylthiourea (0.144 g, 1.09 mmol). The solution was heated to reflux for 14 hours and cooled to room

temperature. The resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with $NaHCO_3$ saturated solution (3 x 10 mL), dried over sodium sulfate, filtered and concentrated yielding 2-butylamino-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (0.319 g, 77%) as an off-white fluffy solid: mp 134-135°C, ^1H NMR (DMSO d_6) 7.94 (t, J = 5.37 Hz, 1 H), 7.78 (d, J = 8.79, 2 H), 7.45-7.36 (m, 4 H), 7.15 (t, J = 8.79 Hz, 2H), 3.25 (q, J = 5.37 Hz, 2 H), 3.18 (s, 3 H), 1.58-1.50 (m, 2 H), 1.41-1.32 (m, 2H), 0.90 (t, J = 7.33 Hz, 3 H); MS (EI) m/z 404 (M+). HRMS Δ = 1.1 mmu.

Example 48

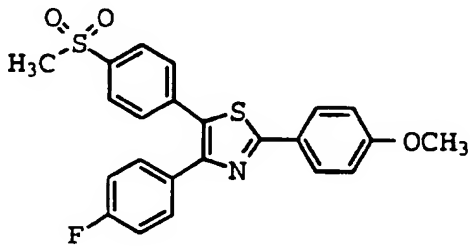


4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-methylaminothiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.355 g, 0.959 mmol) in ethanol (10 mL) was added N-methylthiourea (0.086 g, 0.959 mmol). The solution was heated to reflux for 14 hours and cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in ethyl acetate (100 mL) and washed with $NaHCO_3$ saturated solution (3 x 10 mL), dried over sodium sulfate and filtered. Isooctane was added to the filtrate until the solution became cloudy yielding a pale yellow fluffy solid which was collected by vacuum filtration. This solid was dissolved in methylene chloride and washed with sodium

carbonate solution (10% solution), dried over sodium sulfate, and concentrated yielding a solid. This solid was recrystallized from methylene chloride-isooctane yielding 4-(4-fluorophenyl)-2-methylamino-5-(4-methylsulfonylphenyl)thiazole (0.135 g, 39 %) as a pale yellow powder: mp 243-244°C; ^{1}H NMR 400 MHz 7.90 (q, J = 4.76 Hz, 1 H), 7.81 (d, J = 8.50 Hz, 2 H), 7.49-7.43 (m, 2 H), 7.41 (t, J = 8.70 Hz, 2 H), 7.19 (t, J = 8.95 Hz, 2 H), 3.22 (s, 3 H), 2.90 (d, J = 4.80 Hz, 3 H); MS (FAB) m/z 363 (M+H). HRMS Δ = -0.2 mmu.

Example 49

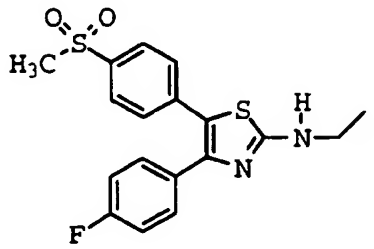


4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(4-methoxyphenyl)thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.500 g, 1.35 mmol) in isopropanol (10 mL) was added *p*-methoxythiobenzamide (0.230 g, 1.35 mmol). The solution was heated to reflux for 30 hours and cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with $NaHCO_3$ saturated solution (3 x 10 mL), dried over sodium sulfate, filtered and concentrated yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(4-methoxyphenyl)thiazole (0.360 g, 61%) as a crystalline solid: mp 187-189°C, ^{1}H NMR ($CDCl_3$) 300 MHz 7.99 (d, 8.82 Hz, 2 H), 7.93 (d, J = 8.50 Hz, 2 H), 7.63-7.53 (m, 4 H), 7.09 (t, J =

8.63 Hz, 2 H), 7.03 (d, J = 8.82 Hz, 2 H), 3.92 (s, 3 H), 3.13 (s, 3 H); MS m/z 440 (M+H). HRMS Δ = 2.0 mmu.

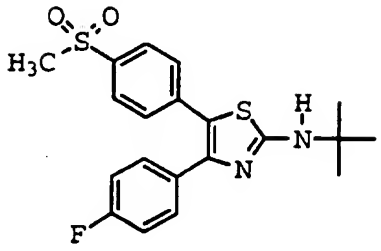
Example 50



2-Ethylamino-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.405 g, 1.09 mmol) in ethanol (10 mL) was added N-ethylthiourea (0.114 g, 1.09 mmol) and the solution was heated to reflux for 14 hours. The reaction was cooled to room temperature and the resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with $NaHCO_3$ saturated solution (3 x 10 mL), sodium carbonate solution (10%, 3 x 20 mL), dried over sodium sulfate, filtered and concentrated. The crude product was recrystallized from methylene chloride and isooctane yielding 2-ethylamino-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (0.218 g, 53%) as a white powdery crystals: mp 218-219°C, ^1H NMR (DMSO d_6) 400 MHz 7.94 (t, 5.38 Hz, 1 H), 7.78 (d, J = 8.56 Hz, 2 H), 7.45-7.40 (m, 2 H), 7.37 (d, J = 8.56 Hz, 2 H), 7.15 (t, J = 9.05 Hz, 2 H), 3.31 (q, J = 7.10 Hz, 2 H), 3.18 (s, 3 H), 1.18 (t, J = 7.10 Hz, 3 H); MS m/z 377 (M+H). HRMS Δ = 0.5 mmu.

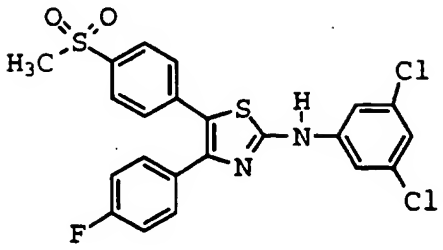
Example 51



2-*tert*-Butylamino-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.406 g, 1.09 mmol) in ethanol (11 mL) was added N-(*tert*-butyl)thiourea (0.144 g, 1.09 mmol) and the solution was heated to reflux (14 hours). The reaction was cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with $NaHCO_3$ saturated solution (3 x 10 mL), sodium carbonate solution (10%, 3 x 20 mL), dried over sodium sulfate, filtered and concentrated. The crude product was recrystallized from methylene chloride and isooctane yielding 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-*tert*-butylaminothiazole (0.226 g, 51%) as a yellow crystalline plates: mp 250-253°C; ^1H NMR (DMSO d_6) 400 MHz 7.78 (d, J = 8.32 Hz, 2 H), 7.70 (s, 1 H), 7.46-7.35 (m, 4 H), 7.15 (t, J = 9.05 Hz, 2 H), 3.19 (s, 3 H), 1.40 (s, 9 H); MS m/z 405 (M+H). HRMS Δ = 4.78 mmu.

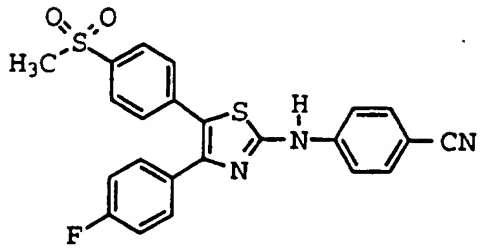
Example 52



2-(3,5-Dichlorophenylamino)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.312, 0.841 mmol) in ethanol (10 mL) was added N-(3,5-dichlorophenyl)thiourea (0.195 g, 0.882 mmol). The solution was heated to reflux (14 hours) and cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in ethyl acetate (100 mL) and washed with sodium carbonate solution (10%, 3 x 20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated, yielding a powdery solid. This solid was dissolved in ethyl acetate/methylene chloride. Addition of isooctane resulted in the precipitation of 2-(3,5-dichlorophenylamino)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (0.261 g, 63%) as a pale yellow powder: mp 287-288°C; ^{1}H NMR (DMSO d_6) 400 MHz 10.84 (s, 1 H), 7.86 (d, J = 8.79 Hz, 2 H), 7.73 (s, 2 H), 7.54-7.45 (m, 4 H), 7.22 (t, J = 8.79 Hz, 2 H), 7.15 (s, 1 H), 3.22 (s, 3 H); MS m/z 492 (M+). HRMS Δ = 4.8 mmu.

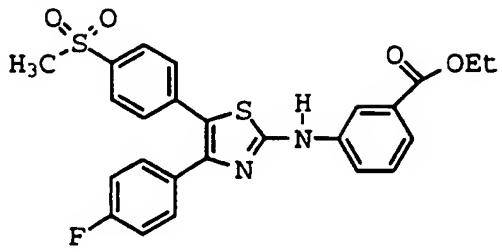
Example 53



2-(4-Cyanophenylamino)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-thiazole

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.413, 1.11 mmol) in ethanol (10 mL) was added N-(4-cyanophenyl)thiourea (0.207 g, 1.17 mmol). The solution was heated to reflux (24 hours) and cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with sodium carbonate solution (10%, 3 x 20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated yielding a solid. This solid was purified by flash chromatography (1:1, hexane:ethyl acetate with 1% acetic acid). The resulting product was recrystallized from methylene chloride and isooctane yielding 2-(4-cyanophenylamino)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (0.266 g, 53%) as a pale yellow solid: mp 273-274°C; ^{1}H NMR (DMSO d_6) 400 MHz 10.98 (s, 1 H), 7.86 (d, J = 8.32 Hz, 2 H), 7.83 (d, J = 9.05 Hz, 2 H), 7.76 (d, J = 8.80 Hz, 2 H), 7.55-7.47 (m, 4 H), 7.21 (t, J = 8.80 Hz, 2 H), 3.22 (s, 3 H); MS m/z 450 (M+H). HRMS Δ = 2.6 mmu.

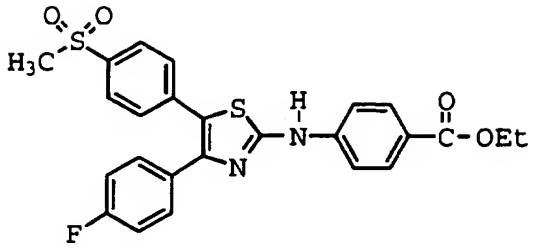
Example 54



Ethyl-[3-[4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]amino]benzoate

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.444, 1.20 mmol) in ethanol (10 mL) was added N-(3-ethoxycarbonylphenyl)thiourea (0.282 g, 1.26 mmol). The solution was heated to reflux (24 hours) and was cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with sodium carbonate solution (10%, 3 x 20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated yielding a solid. The resulting product was recrystallized from methylene chloride and isooctane yielding ethyl[3-[4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]amino]benzoate (0.393 g, 66%) as a pale yellow fluffy solid: mp 208-209°C; ^{1}H NMR (DMSO d_6) 400 MHz 10.68 (s, 1 H), 8.45 (s, 1 H), 7.91-7.84 (m, 3 H), 7.58-7.44 (m, 6 H), 7.19 (t, J = 8.79 Hz, 2 H), 4.30 (q, J = 6.84 Hz. 2 H), 3.21 (s, 3 H), MS m/z 496 (M+). HRMS Δ = 0.03 mmu.

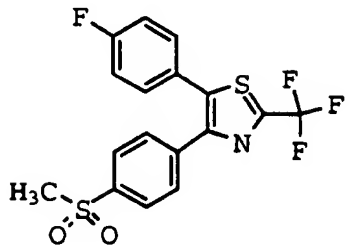
Example 55



Ethyl [4-[4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]amino]benzoate

To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)ethanone (Example 26, Step 2) (0.361, 0.972 mmol) in ethanol (10 mL) was added N-(4-ethoxycarbonylphenyl)thiourea (0.229 g, 1.02 mmol). The solution was heated to reflux (24 hours) and was cooled to room temperature. The resulting suspension was concentrated *in vacuo*, suspended in methylene chloride (100 mL) and washed with sodium carbonate solution (10%, 3 x 20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated yielding a solid. The resulting product was recrystallized from methylene chloride and isooctane yielding ethyl[4-[4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]amino]benzoate (0.277 g, 57%) as a fine, pale yellow crystals: mp 207-208°C; ^{1}H NMR (DMSO-d_6) 400 MHz 10.87 (s, 1 H), 7.93 (d, J = 8.79 Hz, 2 H), 7.87 (d, J = 8.30 Hz, 2 H), 7.78 (d, J = 8.79, 2 H), 7.57-7.49 (m, 4 H), 7.20 (t, J = 9.28 Hz, 2 H), 4.26 (q, J = 7.32 Hz, 2 H), 3.21 (s, 3 H), 1.29 (t, J = 7.32 Hz, 3 H). MS m/z 496 (M+). HRMS Δ = 0.2 mmu.

Example 56



5-(4-Fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole:

Step 1: Preparation of 5-(4-fluorophenyl)-4-(4-methylthiophenyl)-2-trifluoromethylthiazole:

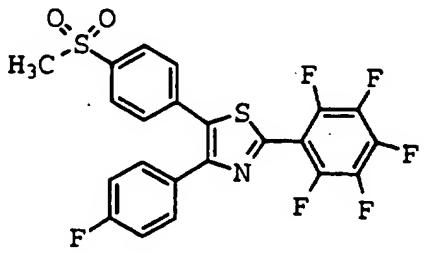
To a solution of trifluoroacetamide (13.7 g, 121.2 mmol) in toluene (30 mL) was added solid P_4S_{10} (5.4 g, 12.1 mmol) and the mixture was heated to reflux for 60 hours. The resulting orange suspension was cooled to room temperature and the solid was pulverized to form a fine suspension. One fourth of this toluene suspension (7.5 mL, ca. 30 mmol of theory) was transferred and 2-bromo-2-(4-fluorophenyl)-1-(4-methylthiophenyl)ethanone (1.24 g, 3.66 mmol) (Example 20, Step 2) was added in one portion. This suspension was heated to reflux for 1.5 hours, cooled to 50°C, and 1.0 N HCl solution (1 mL) was added carefully and heating at reflux continued for 1 hour more. This reaction was cooled to room temperature and let stand overnight. To this solution was added 2 N NaOH solution until the exotherm subsided, and the reaction was stirred for 1 hour longer. The resulting black suspension was diluted with methylene chloride and washed with $NaHCO_3$ saturated solution, dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding a brown semi-solid. Flash chromatography (9:1 hexane:methylene chloride) yielded 5-(4-fluorophenyl)-4-(4-methylthiophenyl)-2-trifluoromethylthiazole (0.28 g, 23%) as yellow oil

which slowly solidified mp: 59-60°C; ^{1}H NMR ($CDCl_3$) 300 MHz 7.43 (d, J = 8.48, 2 H), 7.40-7.32 (m, 2 H), 7.17 (d, J = 8.48 Hz, 2 H), 7.08 (t, J = 8.48, 2 H)2.46 (s, 3 H); MS (EI) m/z 369 (M+H). HRMS Δ = -3.17 mmu.

Step 2: Preparation of 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole:

To a solution of 2-trifluoromethyl-5-(4-fluorophenyl)-4-(4-methylthiophenyl)thiazole from Step 1 (0.25 g, 0.74 mmol) in methylene chloride (10 mL) at 0°C was added MCPBA (0.50 g of 67% peroxide content reagent, 1.9 mmol) in three portions over 2 hours. After 3 hours total reaction time, the reaction was diluted with methylene chloride (150 mL) and this solution was washed with $NaHSO_3$ solution (0.1 M)/$NaHCO_3$ saturated solution (1:1 ratio, 3 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was recrystallized from methylene chloride and isooctane yielding 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (0.19 g, 70%) as opaque white crystals: mp 150-151°C; ^{1}H NMR ($CDCl_3$) 300 MHz 7.89 (d, J = 8.48, 2 H), 7.71 (d, J = 8.85, 2 H), 7.40-7.30 (m, 2 H), 7.13 (t, J = 8.48 Hz, 2 H), 3.06 (s, 3 H); 19F NMR (CDCl3) 300 MHz -61.53, -109.98; MS (EI) m/z 402 (MH+). HRMS Δ = -1.161 mmu.

Example 57



4-(4-Fluorophenyl))-5-(4-methylsulfonylphenyl)-2-(2,3,4,5,6-pentafluorophenyl)thiazol

Step 1: Preparation of pentafluorothiobenzamide:

To a solution of pentafluorobenzamide (5.00 g, 23.69 mmol) in toluene (60 mL) was added Lawesson's reagent (5.70 g, 14.20 mmol). The reaction was heated at reflux overnight, cooled to room temperature, and isooctane (200 mL) was added causing a precipitate to form. The suspension was filtered and the filtrate was concentrated yielding an orange oil which solidified. Flash chromatography of this oil (1:1 hexane:methylene chloride with 2% acetic acid) yielded crude pentafluorothiobenzamide as a white solid (mp 92-93°C) which was used without any further purification.

Step 2: Preparation of 2-pentafluorophenyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole:

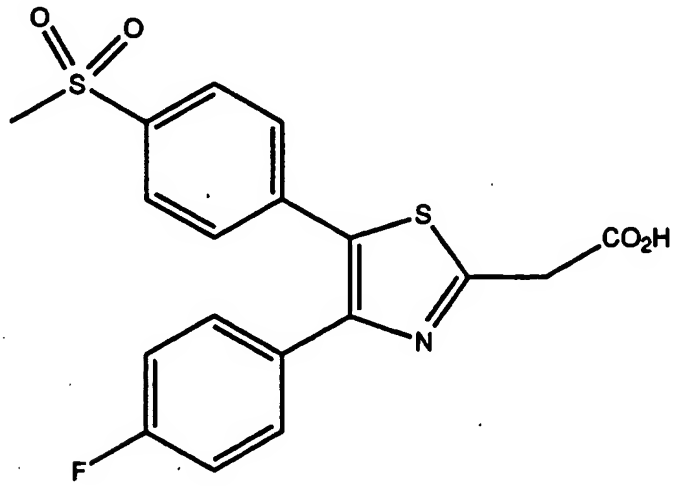
To a solution of 2-bromo-1-(4-fluorophenyl)-2-(4-methylthiophenyl)ethanone (Example 1, Step 3) (3.13 g, 9.22 mmol) in acetonitrile (90 mL) was added pentafluorothiobenzamide from Step 1 (2.2 g, 9.69 mmol) and the mixture was heated to reflux for 16 hours. The resulting burgundy colored reaction solution was poured into hot methanol (400 mL) and the resulting solution was cooled to room temperature yielding a crystalline product. The crystals were collected by vacuum filtration, redissolved in hot acetonitrile and methanol, Darco® decolorizing carbon was added, and the mixture was heated on a steam bath to reflux for two minutes. The resulting black suspension was filtered. The filtrate was diluted with methanol to enhance recrystallization yielding 2-pentafluorophenyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole as papery pale gray crystals (0.59 g, 14 %): mp 131-132°C; ^{1}H NMR ($CDCl_3$) 300 MHz 7.60-7.50 (m, 2 H), 7.31 (d, J = 8.11 Hz, 2 H), 7.23 (d, J = 8.48 Hz, 2 H), 7.02 (t, J = 8.48 Hz, 2 H),

2.52 (s, 3 H); MS (EI) m/z 468 (M+H). HRMS Δ = 1.66 mmu.

Step 3: Preparation of 2-pentafluorophenyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole:

To a solution of 2-pentafluorophenyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)thiazole from step 2 (0.55 g, 1.18 mmol) in methylene chloride (15 mL) at 0°C was added MCPBA (0.51 g of 67% peroxide reagent, 2.94 mmol) and the solution was warmed to room temperature and let stand overnight. The reaction mixture was diluted with methylene chloride (100 mL), washed with $NaHSO_3$ solution (0.1 M), $NaHCO_3$ saturated solution, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was recrystallized from methylene chloride and isooctane yielding 2-pentafluorophenyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (0.48 g, 93%): mp 173-174°C; ^1H NMR ($CDCl_3$) 300 MHz 7.95 (d, J = 8.48 Hz, 2 H), 7.61 (d, J = 8.48, 2 H), 7.52 (d of d, J = 5.16 and 8.48 Hz, 2 H), 7.05 (t, J = 8.48 Hz, 2 H), 3.11 (s, 3 H); ^{19}F NMR ($CDCl_3$) 300 MHz -111.9, -138.8, -150.5, -160.7; MS (EI) m/z 499 (M+H). HRMS Δ = 5.146 mmu.

Example 58



[4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]acetic acid

Step 1: Preparation of [4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-thiazolyl]acetic acid.

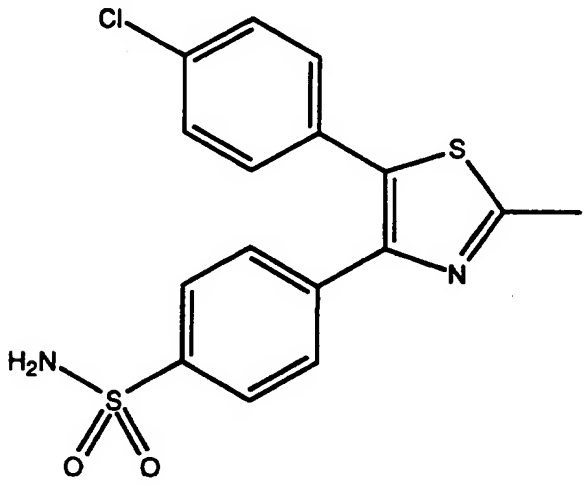
To a stirred solution of 4-[4-fluorophenyl]-2-methyl-5-[4-methylthiophenyl]thiazole (Example 20, Step 3) (0.993 g, 3.15 mmol) in dry tetrahydrofuran (THF) (10 mL) under nitrogen in a dry ice-isopropanol bath was added n-butyllithium (1.4 mL of 2.5 M in hexanes, 3.46 mmol) via syringe. The reaction became an almost opaque dark red color. After 10 minutes, the reaction was poured into a slurry of dry-ice/THF under nitrogen atmosphere. The excess CO_2 was allowed to sublime and the resulting yellow solution was concentrated *in vacuo* yielding a yellow semisolid. This semisolid was dissolved in H_2O (80 mL), washed with hexane and the layers separated. The aqueous phase was poured into 0.05 M HCl solution to give an orange solid. Recrystallization from ethanol/dichloromethane/isooctane yielded [4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-thiazolyl]acetic acid as a solid (0.294 g, 26%): mp 134 °C (dec). ^1H NMR ($CDCl_3$) 300 MHz 7.50-7.42 (m, 2 H), 7.22 (d, J = 8.1 Hz, 2 H), 7.17 (d, J = 8.1 Hz, 2 H), 6.98 (t, J = 8.7 Hz, 2 H), 4.09 (s, 2 H), 2.49 (s, 2H). LRMS: M+H obs. 360. HRMS: M+H Calc'd m/z 360.0528, obs m/z 360.0521. Anal. Calc'd for $C_{18}H_{14}FNO_2S_2$: C, 60.16; H, 3.93, N, 3.90. Found: C, 59.93; H, 3.95; N, 3.88.

Step 2: Preparation of [4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]acetic acid:

To a solution of [4-(4-fluorophenyl)-5-(4-methylthiophenyl)-2-thiazolyl]acetic acid (Step 2)

in ethanol (6 mL) and THF (3 mL) was added a solution of Oxone® (0.575 g, 1.869 mmol) in H_2O (1.5 mL) and reacted for 2 hours. The mixture was diluted with H_2O (100 mL), producing a fine yellow suspension which was collected by vacuum filtration yielding [4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-thiazolyl]acetic acid as a yellow powder (0.199 g, 82%): mp 149-151 °C. ^1H NMR ($CDCl_3$) 300 MHz 7.85 (d, J = 8.66 Hz, 2 H), 7.49 (d, J = 8.66 Hz, 2 H), 7.47-7.36 (m, 2 H), 6.98 (t, J = 8.70 Hz, 2 H), 4.08 (s, 2 h), 3.06 (s, 3 H). LRMS: M+H obs m/z 392; HRMS: M+H Calc'd m/z 392.0427; obs. M+H m/z 392.0419. Anal. Calc'd for $C_{18}H_{14}FNO_4S_2$: C, 55.24; H, 3.61, N, 3.58. Found: C, 55.24; H, 3.70; N, 3.62.

Example 59



4-[5-(4-Chlorophenyl)-2-methyl-4-thiazolyl]benzenesulfonamide

Step 1: Preparation of 2-(4-chlorophenyl)-1-phenylethanone

To a solution of p-chlorophenylacetic acid (14.87 g, 87.16 mmol) in dichloromethane (300 mL) was added dimethylformamide (DMF) (0.5 mL) followed

by careful dropwise addition of oxalyl chloride (8.0 mL, 11.61 g, 91.52 mmol) to maintain a moderate rate of gas evolution. The reaction was stirred for 2 hours, concentrated *in vacuo*, diluted with benzene (150 mL), and $AlCl_3$ was added portionwise. The reaction was heated to reflux overnight. The reaction was cooled to room temperature, was diluted with dichloromethane (150 mL) and poured over ice with stirring. The layers were separated and the dichloromethane phase was filtered, washed with water, $NaHCO_3$ saturated solution, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding the ketone as off white plates (16.72 g, 83%): mp 132-133 °C. ^1H NMR ($CDCl_3$) 300 MHz 8.01 (d, j = 7.05 Hz, 2 H), 7.58 (t, J = 7.86 Hz, 1 H), 7.47 (t, J = 7.86 Hz, 2 H), 7.31 (d, J = 8.46 Hz, 2 H), 7.19 (d, 8.26 Hz, 2 H), 4.26 (s, 2 H).

Step 2: Preparation of 2-bromo-2-(4-chlorophenyl)-1-phenylethanone

To a stirred suspension of 2-(4-chlorophenyl)-1-phenylethanone (Step 1) in HOAc (200 mL) and HBr/HOAc (35 mL, 33 wt%) was added Br_2 (2.3 mL, 7.16 g, 45 mmol). The reaction was stirred for 2 hours and became homogeneous. Water and ethyl ether were added, mixed and the layers separated. The resulting organic phase was washed with water, $NaHCO_3$ saturated solution, brine, dried over $MgSO_4$, filtered, diluted with isooctane and partially concentrated *in vacuo* which caused a precipitate to form. The suspension was filtered to yield the bromoketone as a white solid (10.38 g, 78%) which was suitable for use in the next step without further purification: mp 57-59 °C. ^1H NMR ($CDCl_3$) 300 MHz 7.99 (d, J = 7.25 Hz, 2 HO, 7.59 (t, J =

7.20 Hz, 1 H), 7.46-7.41 (m 4 H), 7.35 (d, J = 8.46 Hz, 2 H), 6.31 (s, 1 H).

Step 3: Preparation of 5-(4-chlorophenyl)-2-methyl-4-phenylthiazole

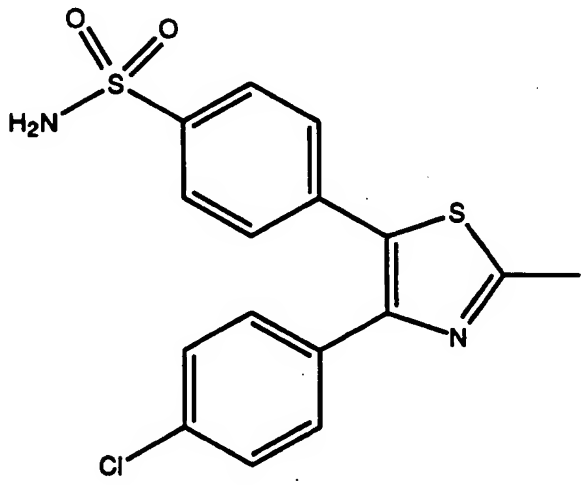
2-Bromo-2-(4-chlorophenyl)-1-phenylethanone (Step 2) (1.10 g, 3.55 mmol) and thioacetamide (0.27 g, 3.55 mmol) were mixed in ethanol (25 mL) and stirred for 48 hours. The reaction was diluted with H_2O and extracted with ethyl acetate. The combined ethyl acetate phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* yielding the thiazole as a clear colorless oil (0.75 g, 74%). ^1H NMR ($CDCl_3$) 300 MHz 7.50-7.44 (m, 2 H), 7.33-7.23 (m, 7H), 2.75 (s, 3 H). LRMS M+H obs 286. Anal. Calc'd for $C_{16}H_{12}ClNS$: C, 67.24; H, 4.23, N, 4.90. Found: C, 66.77; H, 4.23; N, 4.90.

Step 4: Preparation of 4-[2-methyl-4-(5-chlorophenyl)-4-thiazolyl]benzenesulfonamide

To 5-(4-chlorophenyl)-2-methyl-4-phenylthiazole (Step 3) (0.2 g, 0.70 mmol) chilled in an ice bath was added neat chlorosulfonic acid (4 mL). The reaction mixture was warmed to room temperature and reacted for 2 hours. The crude reaction mixture was diluted with dichloromethane (50 mL) and carefully poured over ice with vigorous stirring. The layers were separated and the dichloromethane phase was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was poured into rapidly stirred concentrated NH_4OH (excess) at room temperature and stirred overnight. The layers were separated and the aqueous phase was extracted with more dichloromethane. The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* yielding a solid. The solid

was recrystallized from dichloromethane and isooctane yielding 4-[2-methyl-4-(5-chlorophenyl)-4-thiazolyl]benzenesulfonamide as white plates (0.072 g, 28%): mp 221-223 °C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.84 (d, J = 8.66 Hz, 2 H), 7.64 (d, J = 8.66 Hz, 2 H), 7.32 (d, J = 8.46 Hz, 2 H), 7.23 (d, J = 8.46 Hz, 2 H), 4.76 (br. s, 2 H), 2.76 (s, 3 H). LRMS M+H obs at m/z 365. Anal. Calc'd for $C_{16}H_{13}ClN_2O_2S_2$: C, 52.67; H, 3.59, N, 7.68. Found: C, 52.51; H, 3.63; N, 7.62.

Example 60



4-[4-(4-Chlorophenyl)-2-methyl-5-thiazolyl]benzenesulfonamide

Step 1: Preparation of 4-(4-chlorophenyl)-2-methyl-5-phenylthiazole HBr salt.

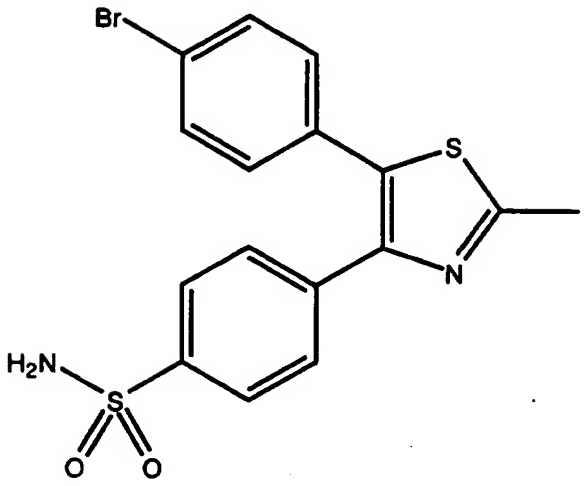
To a stirred solution of 2-bromo-1-(4-chlorophenyl)-2-phenylethanone (Maybridge) (4.58 g, 15.04 mmol) in ethanol (100 mL) and CH_3CN (15 mL) was added thioacetamide (1.186 g, 15.79 mmol) and the mixture was stirred at room temperature for 60 hours. The reaction was concentrated *in vacuo* yielding a yellow oil which crystallized upon standing. The solid was triturated with ethyl

acetate and collected by vacuum filtration yielding 2-methyl-4-(4-chlorophenyl)-5-phenylthiazole HBr salt as a white powder (4.481 g, 81%): mp 192-193 °C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.43 (d, J = 8.66Hz, 2 H), 7.31 (s, 5 H), 7.24 (d, J = 8.46 Hz, 2 H), 2.75 (s, 3 H). LRMS M+H m/z obs 286. HRMS M+H calc m/z 286.0457; obs M+H m/z 286.0448. Anal. Calc'd for $C_{16}H_{12}ClNS \cdot HBr \cdot 1.5\ H_2O$: C, 48.41; H, 3.84, N, 3.55. Found: C, 48.96; H, 3.81; N, 4.00.

Step 2: Preparation of 4-[4-(4-chlorophenyl)-2-methyl-5-thiazolyl]benzenesulfonamide

To vigorously stirred neat chlorosulfonic acid (5 mL) was added 4-(4-chlorophenyl)-2-methyl-5-phenylthiazole (Step 1) (0.56 g, 1.37 mmol). After stirring for 50 minutes, the crude reaction mixture was diluted with dichloromethane (40 mL) and carefully poured over ice. The layers were separated and the dichloromethane layer was poured into concentrated NH_4OH (excess) at room temperature and stirred overnight. The resulting material was diluted with aq $NaHCO_3$, and extracted with dichloromethane and then ethyl acetate. The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* yielding 4-[2-methyl-4-[4-chlorophenyl]-5-thiazolyl]benzenesulfonamide as a white powder (0.275 g, 38%): mp 204-206 °C. ^{1}H NMR ($CDCl_3$) 300 MHz 7.86 (d, J = 8.46 Hz, 2 H), 7.45 (d, J = 8.46 Hz, 2 H), 7.41 (d, J = 8.46, 2 H), 7.29 (d, J = 8.66 Hz, 2 H), 4.81 (br s, 2 H), 2.77 (s, 3 H). LRMS M+H obs 365. HRMS M+H Calc'd m/z 365.0185, M+H obs m/ 365.0198. Anal. Calc'd for $C_{16}H_{13}ClN_2OS_2 \cdot 0.5\ H_2O$: C, 51.51; H, 3.51. Found: C, 51.74; H, 3.67.

Example 61



4-[5-(4-Bromophenyl)-2-methyl-4-thiazolyl]benzenesulfonamide

Step 1: Preparation of 3-(4-bromophenyl)-2-phenylpropenoic acid.

Phenylacetic acid (53.50 g, 393 mmol), 4-bromobenzaldehyde (72.76 g, 393 mmol), triethylamine (43.11 g, 426 mmol), and acetic anhydride (350 mL) were combined and heated to 150 °C for 2 hours and then cooled to 100 °C. Water (120 mL) was slowly added and an exotherm occurred followed by the precipitation of a yellow solid. The solid was collected by vacuum filtration and was recrystallized from toluene (400 mL). The resulting solid was washed with hexanes yielding 3-(4-bromophenyl)-2-phenylpropenoic acid as a light yellow solid (75.07 g, 63%): mp 203-206 °C. ^{1}H NMR (acetone-d_6) 7.80 (s, 1 H), 7.48-7.30 (m, 5 H), 7.28-7.22(m, 2 H), 7.10-7.02 (d, J = 8.46 Hz, 2 H). LRMS M+H obs at m/z 301 and 303.

Step 2: 2-(4-bromophenyl)-1-phenylethanone

To a chilled (ice-bath), stirred solution of 3-[4-bromophenyl]-2-phenylpropenoic acid (Step 1) (65.11 g, 215 mmol) in toluene (300 mL) was added Et_3N (21.98 g, 217 mmol) and DPPA (59.50 g, 216 mmol). The reaction was warmed to room temperature and stirred for over 2 hours. The reaction was poured into water (400 mL) and the layers were separated. The aqueous layer was extracted with Et_2O and the organic phases combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to remove the Et_2O. The resulting suspension was heated to reflux for 1.3 hours causing the evolution of gas. Next, *tert*-butyl alcohol (21 mL, 18.75 g, 253 mmol) was added rapidly and after 40 minutes concentrated HCl (30 mL, 360 mmol) was added dropwise through the condenser over 20 minutes. The reaction was stirred at 110 °C for 1 hour and cooled to room temperature and a precipitate formed. The precipitate was collected by vacuum filtration to yield 2-(4-bromophenyl)-1-phenylethanone as a white solid (20.74 g, 35%). A second crop was obtained by concentrating the filtrate *in vacuo* and recrystallizing the residue from ethyl acetate/hexane to yield an additional 12.07 g (20%): mp 141-144 °C. ^1H NMR (acetone-d_6) 8.07 (d, J = 7.25 Hz, 2 H), 7.71-7.45 (m, 5 H), 7.28 (d, J = 8.46 Hz, 2 H), 4.40 (s, 2 H). LRMS M+Li obs at m/z 281.

Step 3: Preparation of 2-bromo-2-(4-bromophenyl)-1-phenylethanone

To a stirred suspension of 2-(4-bromophenyl)-1-phenylethanone (Step 2) (20.59 g, 74.8 mmol) in HOAc (150 mL) and HBr/HOAc (30 wt%, 25 mL) was added Br_2 (4 mL, 77.6 mmol) and within 1 hour the

reaction became homogeneous. After 1.75 hours, the reaction suspension was filtered yielding a white solid and filtrate. The filtrate was treated with 10% $NaHSO_3$ until the Br_2 color was extinguished and a precipitate formed which was collected and combined with the above solid. This solid was dissolved in ethyl acetate, washed with water, 10 % $NaHSO_3$, saturated, $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding a white solid (20.42 g, 77 %): ^1H NMR (acetone-d_6) 8.13 (d, J = 8.26 Hz, 2 H), 7.75-7.50 (m, 7 H), 6.94 (s, 1 H). LRMS M+Li obs at m/z 359/361/363.

Step 4: Preparation of 5-[4-bromophenyl]-2-methyl-4-phenylthiazole

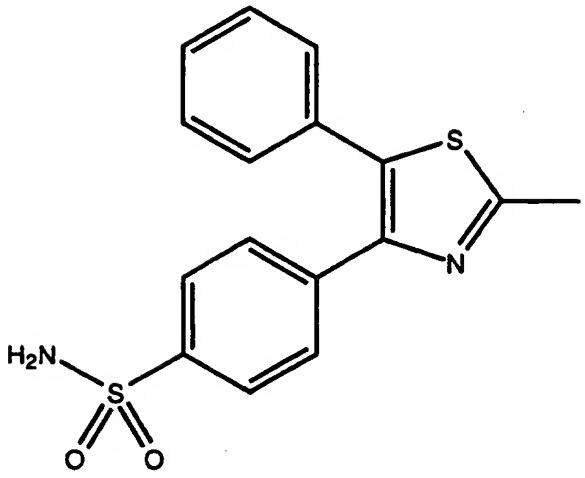
To a stirred solution of 2-bromo-2-(4-bromophenyl)-1-phenylethanone (Step 3) (2.04 g, 5.80 mmol) in EtOH (40 mL) was added thioacetamide (0.46 g, 6.09 mmol) and the solution was stirred for 24 hours. The reaction was concentrated *in vacuo*, the residue dissolved in dichloromethane (125 mL) and washed with saturated $NaHCO_3$ solution (3 X 25 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding an oil. The oil was purified by flash chromatography (hexanes:EtOAc, 10:1) yielding 5-(4-bromophenyl)-2-methyl-4-phenylthiazole (1.262 g, 66%) as a clear colorless oil which was sufficiently pure to utilize in the next step: ^1H NMR ($CDCl_3$) 7.50-7.45 (m, 2 H), 7.43 (d, J = 8.66 Hz, 2 H), 7.33-7.26 (m, 3 H), 7.18 (d, J = 8.46 Hz, 2 H), 2.75 (s, 3 H).

Step 5: Preparation of 4-[5-(4-bromophenyl)-2-methyl-4-thiazolyl]benzenesulfonamide

To neat chlorosulfonic acid (10 mL) under nitrogen, chilled to -12 °C in a NaCl/ice bath was

added 5-[4-bromophenyl]-2-methyl-4-phenylthiazole (Step 4) (1.00 g, 3.03 mmol) dropwise as a warm moderately viscous oil. After 2 hours at -10 °C, the reaction was warmed to 0 °C and stirred for 1.5 hours. The clear green reaction solution was poured over ice yielding a precipitate which was collected by vacuum filtration. This solid was dissolved in dichloromethane (75 mL), mixed with concentrated NH_4OH (8 mL) at 0°C and stirred for 2 hours. The reaction was diluted with dichloromethane (50 mL) and brine (50 mL). The layers were separated, and the organic phase washed with 1 N HCl, $NaHCO_3$ (saturated aq), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding a pale yellow solid. This solid was recrystallized from ethyl acetate/hexane yielding 4-[2-methyl-5-(4-bromophenyl)-4-thiazolyl]benzenesulfonamide as a white powder (0.232 g, 19%): mp 207-209 °C. ^1H NMR ($CDCl_3$) 300 MHz 7.83 (d, J = 8.66 Hz, 2 H), 7.63 (d, J = 8.66 Hz, 2 H), 7.47 (d, J = 8.66 Hz), 7.17 (d, J = 8.66 Hz, 2 H), 4.85 (br s, 2 H), 2.77 (s, 3 H). LRMS M+H obs at m/z 409. HRMS M+H Calc'd m/z 408.968, M+H obs m/z 408.9681. Anal. Calc'd for $C_{16}H_{13}BrN_2O_2S_2 \cdot 1.5\ H_2O$ C, 44.04; H, 3.00; N, 6.42. Found: C, 44.20; H, 3.40; N, 6.53.

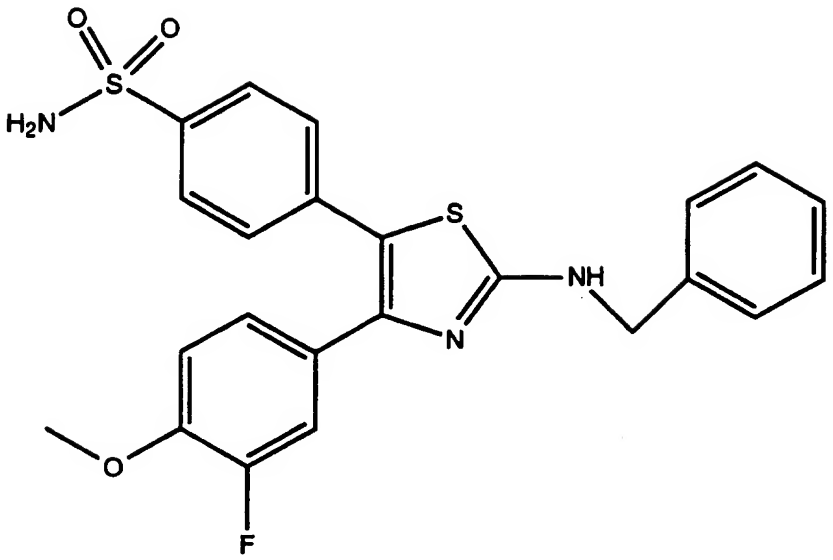
Example 62



4-(2-Methyl-5-phenyl-4-thiazolyl)benzenesulfonamide

To a solution of 4-[2-methyl-5-(4-bromophenyl)-4-thiazolyl]benzenesulfonamide (Example 61) in methanol (10 mL), THF (2 mL), and HOAc (0.5 mL) was added 5% Pd/C (0.060 g). The reaction was charged with H_2 (50 psi) and stirred overnight. The suspension was filtered through diatomaceous earth. The filtrate was concentrated *in vacuo* yielding 4-(2-methyl-5-phenyl-4-thiazolyl)benzenesulfonamide as a solid (0.134 g, 52%): mp 238-239 °C. ^1H NMR (CD_3OD) 300 MHz 7.86 (d, J = 8.46 Hz, 2 H), 7.61 (d, J = 8.46 Hz, 2 H), 7.46-7.27 (m, 5 H), 2.85 (s, 3 H). LRMS (M+H obs at m/z 331). HRMS M+H Calc'd m/z 331.0575, obs M+H m/z 331.0566.

Example 63



4-[2-Benzylamino-4-(3-fluoro-4-methoxyphenyl)-5-thiazolyl]benzenesulfonamide

Step 1: Preparation of 1-(4-methoxy-3-fluorophenyl)-2-phenylethanone

To a chilled (ice bath) suspension of 2-fluoroanisole (35.90 g, 0.285 mol) and $AlCl_3$ (37.95 g, 0.285 mol) in chloroform ($CHCl_3$) (500 mL) was added phenylacetyl chloride dropwise maintaining the temperature below 5 °C. After stirring for 2 hours, the reaction was poured over ice, the layers separated, and the organic phase was washed with 1 N HCl, brine, and water, dried over $MgSO_4$, filtered and concentrated. The crude product was recrystallized from ethyl acetate/hexane yielding 1-(4-methoxy-3-fluorophenyl)-2-phenylethanone a white solid (65 g, 93 %) which was used without further purification.

Step 2: Preparation of 1-(4-methoxy-3-fluorophenyl)-2-(4-aminosulfonylphenyl)ethanone

To 1-(4-methoxy-3-fluorophenyl)-2-phenylethanone (Step 1) (65 g, 0.266 mol) was added chlorosulfonic acid (150 mL, 263 g, 2.25 mol) and the solution was stirred for 3 hours. This solution was carefully poured dropwise over ice and the aqueous phase was extracted with dichloromethane. The dichloromethane phase was added to rapidly stirred NH_4OH (concentrated 200 mL) and the mixture was stirred overnight. The resulting suspension was filtered and the solid was triturated with hot acetone yielding the sulfonamide as a light yellow solid (12.0 g, 14 %) which was used without further purification.

Step 3: Preparation of 2-bromo-1-(4-methoxy-3-fluorophenyl)-2-(4-aminosulfonylphenyl)-ethanone

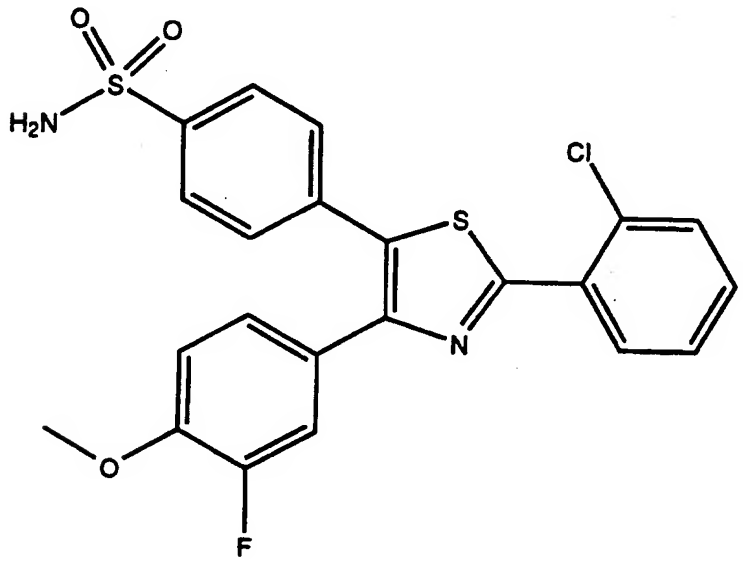
To a mixture of 1-[4-methoxy-3-fluorophenyl]-2-(4-aminosulfonylphenyl)-ethanone (11.4 g, 0.035 mol) in HOAc (200 mL) and HBr in HOAc (33 % solution, 50 mL) was added Br_2 (5.6 g, 0.035 mol). The mixture was heated at reflux for 4 hours, cooled to room temperature, and poured into water yielding the crude bromo ketone as a white precipitate (12.1 g, 90 %) which was used without further purification: mp 137-141 °C.

Step 4: Preparation of 4-[2-benzylamino-4-(3-fluoro-4-methoxyphenyl)-5-thiazolyl]benzenesulfonamide

To a stirred solution of 2-bromo-1-(4-methoxy-3-fluorophenyl)-2-(4-aminosulfonylphenyl)-ethanone (Step 3) (0.383 g, 0.952 mmol) in CH_3CN (5 mL) was added N-benzylthiourea (0.158 g, 0.952 mmol) in one portion and the reaction was stirred for 60 hours at room temperature. The reaction was concentrated *in vacuo* and partitioned between ethyl acetate and H_2O. The ethyl acetate phase was dried over $MgSO_4$,

filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with hexanes:ethyl acetate (2:1) yielding 4-[2-benzylamino-4-[3-fluoro-4-methoxyphenyl]-5-thiazolyl]benzenesulfonamide as a solid (0.161 g, 36%): mp 199-200 °C. ^{1}H NMR ($CDCl_3$/DMSO-d_6) 300 MHz 7.76 (d, J = 8.66 Hz, 2 H), 7.42-7.28 (m, 7 H), 7.26-7.21 (m, 1H), 7.16-7.09 (m, 1 H), 6.82 (t, J = 8.98 Hz, 1 H), 5.89 (br t, J = 5.64, 1 H), 5.62 (s, 2 H), 4.51 (d, J = 5.64 Hz, 2 H), 3.87 (s, 3 H). LRMS M+H obs at m/z 470. HRMS M+H calc m/z 470.1008, obs m/z 470.1022.

Example 64

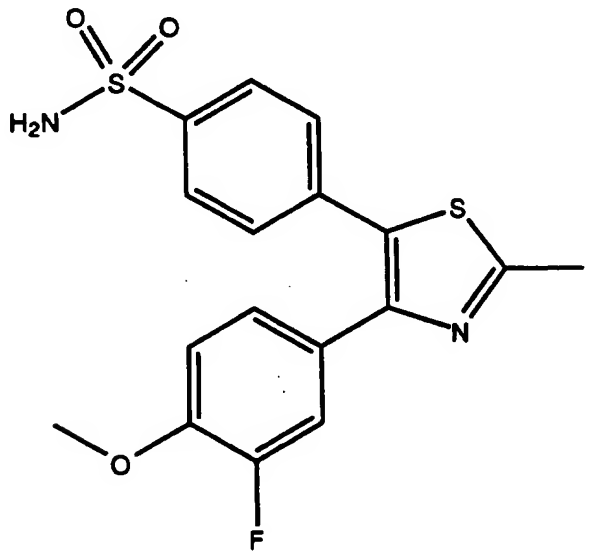


4-[2-[2-Chlorophenyl]-4-[3-fluoro-4-methoxyphenyl]-5-thiazolyl]benzenesulfonamide

To a stirred solution of 2-bromo-1-(4-methoxy-3-fluorophenyl)-2-(4-aminosulfonylphenyl)ethanone (0.387 g, 0.962 mmol) (Example 63, Step 3) in CH_3CN (5 mL) was added o-chlorothiobenzamide (0.165 g, 0.962 mmol) in one portion and the reaction mixture was stirred for 60 hours at room temperature . The

yellow suspension was concentrated *in vacuo*. The solid was suspended in ethanol and collected by vacuum filtration yielding 4-[2-(2-chlorophenyl)-4-(3-fluoro-4-methoxyphenyl)-5-thiazolyl]benzenesulfonamide as a pale yellow solid (0.147 g, 32%): mp 214-216 °C. ^{1}H NMR ($CDCl_3$/DMSO-d_6) 300 MHz 7.85 (d, J = 8.26 Hz, 2 H), 7.75-7.72 (m, 1 H), 7.71-7.64 (m, 1 H), 7.52-7.42 (m, 2 H), 7.38-7.30(m, 4 H), 6.97 (t, J = 8.24 Hz, 1 H), 5.85 (br s, 2 H), 3.92 (s, 3 H). LRMS M+H obs at m/z 475. HRMS M+H Calc'd m/z 475.0353; M+H obs m/z 475.0352.

Example 65

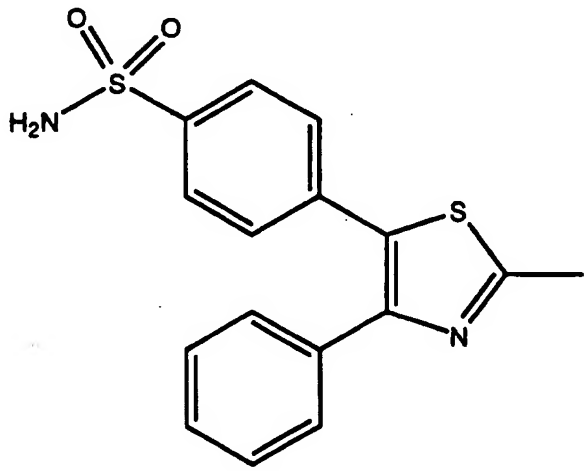


4-[4-(3-Fluoro-4-methoxyphenyl)-2-methyl-5-thiazolyl]benzenesulfonamide

To a stirred solution of 2-bromo-1-(4-methoxy-3-fluorophenyl)-2-(4-aminosulfonylphenyl)ethanone (0.440 g, 0.1.094 mmol) (Example 63, Step 3) in CH_3CN (5 mL) was added thioacetamide (0.082 g, 1.094 mmol) in one portion and the reaction was stirred for 60 hours at room temperature. The reaction was concentrated *in vacuo* and partitioned

between ethyl acetate and H_2O. The ethyl acetate phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with hexanes:ethyl acetate (1:1), yielding 4-[2-methyl-4-[3-fluoro-4-methoxyphenyl]-5-thiazolyl]benzenesulfonamide as a solid (0.061 g, 15%): mp 168-175 °C. ^1H NMR ($CDCl_3$) 300 MHz 7.87 (d, J = 8.66 Hz, 2 H), 7.46 (d, J = 8.66 Hz, 2 H), 7.29-7.22 (m, 1 H), 7.17-7.12 (m, 1 H), 6.87 (t, J = 9.07, 1 H), 4.82 (br s, 2 H), 3.90 (s, 3 H), 2.76 (s, 3 H). LRMS M+H obs at m/z 379. HRMS M+H calc m/z 379.0586, M+H obs m/z 379.0605. Anal. Calc'd for $C_{17}H_{15}FN_2O_3S_2$, C, 53.96; H, 4.00; Found C, 53.69; H, 4.17.

Example 66



4-(2-Methyl-4-phenyl-5-thiazolyl)benzenesulfonamide

Step 1: Preparation of 2-methyl-3,4-diphenylthiazole

To a suspension of lithium chloride (12.56 g, 296.35 mmol) and benzoin (12.58 g, 59.27 mmol) in DMF (100 mL) was added Et_3N (9.0 g, 88.90 mmol).

The reaction was cooled with a water bath and methanesulfonyl chloride (6.9 mL, 10.18 g, 88.9 mmol) was added over 0.08 hour. The reaction became a pale yellow suspension. After stirring for 2 hours, additional Et_3N (9.0 g, 88.90 mmol) and methanesulfonyl chloride (6.9 mL, 10.18 g, 88.9 mmol) were added. In 2 hours, the reaction was complete and was diluted with Et_2O (500 mL), washed with brine, dried over Na_2SO_4, filtered and concentrated yielding an orange oil. This oil was dissolved in ethanol (120 mL) and thioacetamide added and the reaction was stirred at room temperature for 5 days, then heated to reflux for 2 hours. The reaction was cooled to room temperature, diluted with H_2O, yielding an oily product. This oil was purified by flash chromatography, yielding an oil which slowly crystallized to form an orange solid (1.81 g, 12%). This material was suitable to use without further purification: mp 45-49 °C. ^1H NMR ($CDCl_3$) 300 MHz 7.57-7.48 (m, 2 H), 7.35-7.26 (m, 8 H), 2.76 (s, 3 H).

Step 2: Preparation of 4-(2-methyl-4-phenyl-5-thiazolyl)benzenesulfonamide

To stirred chlorosulfonic acid (1.3 mL, 19.89 mmol) chilled in a NaCl/ice bath was added 3,4-diphenyl-2-methylthiazole (Step 1) (1.00 g, 3.98 mmol). The reaction was warmed to room temperature and stirred for 2 hours. Additional chlorosulfonic acid (4 mL) was added and the reaction proceeded at room temperature for 0.5 hour. The dark mixture was carefully poured over ice. The aqueous phase was decanted from the oily layer and was extracted with dichloromethane. The organic phase was combined with the oily residue and poured into concentrated NH_4OH. After 4 hours, the mixture was

diluted with dichloromethane, the layers separated, and the dichloromethane phase washed with aq $KHSO_4$ solution, aq $NaHCO_3$, brine, filtered and concentrated *in vacuo* yielding an orange solid. This solid was triturated with dichloromethane and collected by vacuum filtration yielding 4-(2-methyl-4-phenyl-5-thiazolyl)benzenesulfonamide as a tan solid (0.432 g, 33%): mp 212-214 °C. ^1H NMR ($CDCl_3$ with CD_3OD) 300 MHz 7.81 (d, J = 8.66 Hz, 2 H), 7.46-7.38 (m, 4 H), 7.33-7.27 (m, 3 H), 5.42 (br s, <1/ partially exchanged), 2.76 (s, 3 H). LRMS M+H obs at m/z 331. HRMS M+H Calc'd m/z 331.0575, obs M+H m/z 331.0561.

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 ml) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 ml of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the

percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in *Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

Rat Carrageenan-induced Analgesia Test

The rat carrageenan analgesia test was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, **32**, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table I.

TABLE I.

	RAT PAW EDEMA % Inhibition @ 20mg/kg body weight	ANALGESIA % Inhibition @ 20mg/kg body weight
Examples		
8	12	-
10	14	-
12	53	-
16	50	27
20	48	-
23	39.5	-
24	20*	-
29	42	24
31	27.5*	-
33	36	34[a]
35	16	-
37	9	-
39	19	-
41	4	-
45	19*	-
46	25*	-
47	12	-
48	15*	-
49	6*	-
50	11*	-
51	14*	-
52	7*	-
56	20*	-
57	2*	-

* @ 10mg/kg

a @ 30mg/kg

Evaluation of COX I and COX II activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX II. The COX II inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

Recombinant COX-1 and COX-2 were prepared as described by Gierse et al, [*J. Biochem.*, **305**, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10^7 - 10^8 pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5×10^6/ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX I and COX II activity:

COX activity was assayed as PGE_2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37°C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE_2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table II.

TABLE II.

	Species murine (m)/human (h)	COX I ID_{50} µM	COX II ID_{50} µM
Examples			
1	m	>100	0.1
	h	>10	<0.1
2	h	>100	<0.1
3	h	>100	<0.1
4	m	6.2	<0.1
	h	70	<0.1
5	h	>100	<0.1
6	h	>100	<0.1
7	h	>100	<0.1
8	m	>100	0.2
9	h	>100	<0.1
10	h	>100	<0.1
11	h	>100	<0.1

TABLE II. (cont.)

Species murine (m)/human (h)		COX I ID_{50} μM	COX II ID_{50} μM
Examples			
12	m	1.6	<0.1
	h	>10	<0.1
13	m	>30	1.2
14	m	39.8	0.5
	h	>100	0.6
15	h	>100	0.2
16	m	>10	<0.1
	h	>100	<0.1
17	m	>10	0.3
18	m	5.4	0.1
19	m	.4	<0.1
20	m	>10	0.1
21	m	>10	<0.1
	h	>10	<0.1
22	m	>100	11.2
23	m	.7	<0.1
	h	1.1	<0.1
24	m	>10	<0.1
25	h	2.6	<0.1
26	m	>100	0.5
27	m	>10	0.2
28	m	>10	<0.1
29	m	.5	0.1
30	m	.9	0.3
31	m	>10	0.1
32	h	0.7	<0.1
33	h	>100	<0.1
34	h	<0.1	<0.1
35	m	>100	<0.1
36	h	>100	<0.1
37	m	>100	<0.1

TABLE II. (cont.)

	Species murine (m)/human (h)	COX I ID_{50} μM	COX II ID_{50} μM
Examples			
38	h	>100	<0.1
39	m	>10	0.3
40	h	>100	<0.1
41	h	>100	<0.1
42	m	1.9	<0.1
43	m	100	1.3
44	m	1.7	<0.1
45	m	>100	<0.1
46	m	1.4	<0.1
47	m	1.4	<0.1
48	m	>10	0.3
49	m	>10	0.3
50	m	>10	0.3
51	m	11.9	0.3
52	m	>100	0.5
53	m	0.2	0.9
54	m	1.1	1.3
55	m	>10	3.5
56	m	>100	<0.1
56	h	>100	<0.1
57	m	4.9	<0.1
	h	>100	<0.1
58	h	>100	0.3
59	h	35.6	<0.1
61	h	100	<0.1
63	h	<0.1	<0.1
64	h	2.5	>100

Biological paradigms for testing the cytokine-inhibiting activity of these compounds are found in WO95/13067, published 18 May 1995.

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.5 and about 20 mg/kg body

weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In

the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

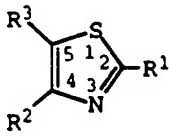
Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula I



I

wherein R^1 is selected from hydrido, halo, amino, alkoxy, cyano, nitro, hydroxyl, aminocarbonyl, acyl, alkylaminocarbonyl, arylaminocarbonyl, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, carboxyl, carboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylaminoalkyl, heterocycloalkyl, aralkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, N-alkylsulfonylamino, heteroarylsulfonylalkyl, heteroarylsulfonylhaloalkyl, aryloxyalkyl, aralkyloxyalkyl, aryl and heterocyclo, where the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, haloalkyl, haloalkoxy, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, amino, acyl and alkylamino; and

wherein R^2 and R^3 are independently selected from alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^2 and R^3 are optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aminosulfonyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, alkoxyalkyl, hydroxyalkyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, heterocyclic and nitro;

provided one of R^2 and R^3 is aryl substituted with alkylsulfonyl, haloalkylsulfonyl or aminosulfonyl; further provided that R^2 is not 4-fluorophenyl when R^1 is methyl and R^3 is 4-methylsulfonylphenyl; further provided that R^3 is not 4-fluorophenyl when R^1 is methyl and R^2 is 4-aminosulfonylphenyl; further provided R^2 and R^3 are not phenyl substituted with α,α-bis(methyl)methanol; and further provided that R^2 is not 4-(methylsulfonyl)phenyl when R^1 is α,α-bis(trifluoromethyl)methanol;

or a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein R^1 is selected from hydrido, halo, amino, lower alkoxy, cyano, nitro, hydroxyl, aminocarbonyl, acyl, lower alkylaminocarbonyl, phenylaminocarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, phenylamino, lower aralkylamino, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminoalkyl, lower heterocycloalkyl, lower aralkyl, lower cyanoalkyl, lower N-alkylsulfonylamino, lower heteroarylsulfonylalkyl, lower heteroarylsulfonylhaloalkyl, lower aryloxyalkyl, lower aralkyloxyalkyl, aryl and heterocyclo, wherein the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino; and wherein R^2 and R^3 are independently selected from lower alkyl, lower alkenyl, aryl, lower cycloalkyl, lower cycloalkenyl and heterocyclic; wherein R^2 and R^3 are optionally substituted at a substitutable position with one or more radicals

selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkenyl, lower alkynyl, cyano, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, acyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, heterocyclic and nitro; or a pharmaceutically-acceptable salt thereof.

3. Compound of Claim 2 wherein R^1 is selected from fluoro, chloro, bromo, iodo, amino, methoxy, ethoxy, propoxy, butoxy, isopropoxy, *tert*-butoxy, cyano, nitro, hydroxy, aminocarbonyl, formyl, acetyl, N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methyl-N-phenylaminocarbonyl, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, ethylenyl, propylenyl, butenyl, pentenyl, isopropylenyl, isobutylenyl, propargyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, N-methylamino, N-ethylamino, N-propylamino, N-butylamino, N-*tert*-butylamino, N-pentylamino, N-hexylamino, N,N-dimethylamino, carboxyl, N-benzylamino, 3,5-dichlorophenylamino, 3,5-dichlorophenoxymethyl, 3-chlorophenoxymethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, methylaminomethyl, morpholinomethyl, pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, pyridylmethyl, thienylmethyl, benzyl, phenethyl, phenylpropyl, cyanomethyl, phenoxymethyl, benzyloxymethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl,

tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, N-methylsulfonylamino, (2-thienyl)sulfonylmethyl, (2-thienyl)sulfonylbromomethyl, phenyl optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, methoxy, ethoxy, propoxy, butoxy, isopropoxy, *tert*-butoxy, methylthio, methylsulfinyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, amino, formyl, methylamino and dimethylamino, and heterocyclic selected from morpholino, pyrrolidinyl, piperazinyl, piperidinyl, pyridyl, thienyl, thiazolyl, oxazolyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, imidazolyl, and benzimidazolyl, furyl, pyrrolyl, pyrazolyl and triazolyl, optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, methoxy, ethoxy, propoxy, butoxy, isopropoxy, *tert*-butoxy, methylthio, methylsulfinyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, amino, formyl, methylamino and dimethylamino; and wherein R^2 and R^3 are independently selected from methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, ethylenyl, propylenyl, butenyl, pentenyl,

isopropylenyl, isobutylenyl, phenyl, naphthyl, biphenyl, pyridyl, thienyl, thiazolyl, oxazolyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolinyl, imidazolyl, benzimidazolyl, furyl, pyrrolyl, pyrazolyl, triazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, morpholino, pyrrolidinyl, piperazinyl and piperidinyl; wherein R^2 and R^3 are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, ethylenyl, propylenyl, butenyl, pentenyl, isopropylenyl, isobutylenyl, propargyl, cyano, carboxyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, formyl, acetyl, N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methyl-N-phenylaminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, ethoxy, propoxy, butoxy, isopropoxy, *tert*-butoxy, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, pyridyl, furyl, pyrazinyl, pyrrolyl, pyrazolyl, morpholino, pyrrolidinyl, piperazinyl, piperidinyl, triazolyl and nitro; or a pharmaceutically-acceptable salt thereof.

4. Compound of Claim 3 selected from compounds, and their pharmaceutically-acceptable salts or prodrugs, of the group consisting of

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(4-pyridyl)thiazole;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

2-((3-chlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-(2-methyl-4-thiazolyl)thiazole;

4-(4-fluorophenyl)-2-[(4-methoxyphenoxy)methyl]-5-[4-(methylsulfonyl)phenyl]thiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-phenylthiazole;

4-(4-fluorophenyl)-2-n-hexylamino-5-(4-methylsulfonylphenyl)thiazole;

2-butylamino-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-methylaminothiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(4-methoxyphenyl)thiazole;

2-ethylamino-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-thiazole;

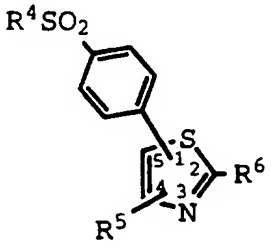
2-*tert*-butylamino-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

2-(3,5-dichlorophenylamino)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole; and

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2,3,4,5,6-pentafluorophenyl)thiazole.

5. A compound of Formula II



II

wherein R^4 is selected from alkyl and amino;

wherein R^5 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aminosulfonyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, heterocyclic and nitro; and

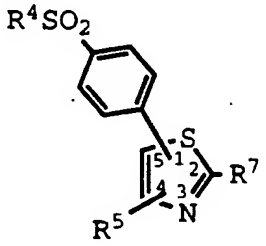
wherein R^6 is selected from halo, amino, alkoxy, nitro, hydroxyl, aminocarbonyl, acyl, alkylaminocarbonyl, arylaminocarbonyl, alkenyl, alkynyl, haloalkoxy, alkylamino, arylamino,

aralkylamino, alkoxycarbonylalkyl, alkylaminoalkyl, heterocycloalkyl, aralkyl, cyanoalkyl, N-alkylsulfonylamino, heteroarylsulfonylalkyl, heteroarylsulfonylhaloalkyl, aryloxyalkyl, aralkyloxyalkyl, aryl and heterocyclo, wherein the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, haloalkyl, haloalkoxy, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, amino, acyl and alkylamino; or a pharmaceutically-acceptable salt thereof.

6. Compound of Claim 5 wherein R^4 is selected from lower alkyl and amino; wherein R^5 is selected from aryl, lower cycloalkyl, lower cycloalkenyl and heteroaryl; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower haloalkylsulfonyl, aminosulfonyl, lower alkyl, lower alkenyl, lower alkynyl, cyano, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, acyl, lower N-alkylaminocarbonyl, lower N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, heterocyclic and nitro; and wherein R^6 is selected from halo, amino, lower alkoxy, nitro, hydroxyl, aminocarbonyl, acyl, lower alkylaminocarbonyl, lower arylaminocarbonyl, lower alkenyl, lower alkynyl, lower haloalkoxy, lower alkylamino, phenylamino, lower aralkylamino, lower alkoxycarbonylalkyl, lower alkylaminoalkyl, lower heterocycloalkyl, lower aralkyl, lower cyanoalkyl, lower N-alkylsulfonylamino, lower

heteroarylsulfonylalkyl, lower heteroarylsulfonylhaloalkyl, lower aryloxyalkyl, lower aralkyloxyalkyl, phenyl optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino, and heterocyclic optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino; or a pharmaceutically-acceptable salt thereof.

7. A compound of Formula III



III

wherein R^4 is selected from alkyl and amino;

wherein R^5 is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aminosulfonyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy,

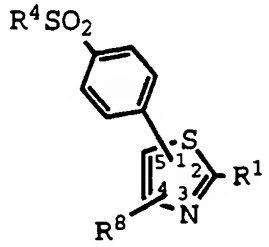
amino, N-alkylamino, N,N-dialkylamino, heterocyclic and nitro; and

wherein R^7 is selected from hydrido, alkyl, haloalkyl, cyano, hydroxyalkyl, alkoxyalkyl, carboxyl, carboxyalkyl, and alkoxycarbonyl;

provided that R^5 is not 4-fluorophenyl when R^7 is methyl; further provided R^5 is not phenyl substituted with α,α-bis(methyl)methanol; and further provided that R^4 is not methyl when R^7 is α,α-bis(trifluoromethyl)methanol; or a pharmaceutically-acceptable salt thereof.

8. Compound of Claim 7 wherein R^4 is selected from lower alkyl and amino; wherein R^5 is selected from aryl, lower cycloalkyl, lower cycloalkenyl and heteroaryl; wherein R^5 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower haloalkylsulfonyl, aminosulfonyl, lower alkyl, lower alkenyl, lower alkynyl, cyano, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, acyl, lower N-alkylaminocarbonyl, lower N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, heterocyclic and nitro; and wherein R^7 is selected from hydrido, lower alkyl, lower haloalkyl, cyano, lower hydroxyalkyl, lower alkoxyalkyl, carboxyl, lower carboxyalkyl, and lower alkoxycarbonyl; or a pharmaceutically-acceptable salt thereof.

9. A compound of Formula IV



IV

wherein R^1 is selected from hydrido, halo, amino, alkoxy, cyano, nitro, hydroxyl, aminocarbonyl, acyl, alkylaminocarbonyl, arylaminocarbonyl, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, carboxyl, carboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylaminoalkyl, heterocycloalkyl, aralkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, N-alkylsulfonylamino, heteroarylsulfonylalkyl, heteroarylsulfonylhaloalkyl, aryloxyalkyl, aralkyloxyalkyl, aryl and heterocyclo, wherein the aryl and heterocyclo radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, haloalkyl, haloalkoxy, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, amino, acyl and alkylamino;

wherein R^4 is selected from alkyl and amino; and

wherein R^8 is heterocyclic; wherein R^8 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, alkenyl, alkynyl, cyano, carboxyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, acyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, and nitro;

or a pharmaceutically-acceptable salt thereof.

10. Compound of Claim 9 wherein R^1 is selected from hydrido, halo, amino, lower alkoxy, cyano, nitro, hydroxyl, aminocarbonyl, acyl, lower alkylaminocarbonyl, phenylaminocarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, phenylamino, lower aralkylamino, carboxyl, lower carboxyalkyl, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminoalkyl, lower heterocycloalkyl, lower aralkyl, lower hydroxyalkyl, lower alkoxyalkyl, lower cyanoalkyl, lower N-alkylsulfonylamino, lower heteroarylsulfonylalkyl, lower heteroarylsulfonylhaloalkyl, lower aryloxyalkyl, aralkyloxyalkyl, aryl optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino, and heterocyclic optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower haloalkyl, lower haloalkoxy, lower carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, amino, acyl and lower alkylamino; wherein R^4 is selected from lower alkyl and amino; and wherein R^8 is nitrogen-containing heteroaryl optionally substituted at a substitutable position with one or more substituents independently selected from halo, alkyl, alkoxy, alkylthio, amino and alkylamino; or a pharmaceutically-acceptable salt thereof.

11. Compound of Claim 10 wherein R^1 is selected from hydrido, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *tert*-butyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl,

dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyanomethyl, cyanoethyl, cyanopropyl, methylamino, ethylamino, propylamino, butylamino, *tert*-butylamino, pentylamino, hexylamino, phenethyl, phenylpropyl, benzyl, phenylamino, thienylsulfonylmethyl, thienylsulfonylbromomethyl, benzylamino, phenoxymethyl, 3,5-dichlorophenylamino, 3,5-dichlorophenoxymethyl, 3-chlorophenoxymethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, phenyl optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methoxy, ethoxy, propoxy, butoxy, isopropoxy and *tert*-butoxy, and a heterocyclic radical selected from thienyl, pyridyl, furyl, oxazolyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolinyl, imidazolyl, thiazolyl, pyrrolyl, pyrazolyl and triazolyl, optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl and *tert*-butyl; wherein R^4 is methyl or amino; and wherein R^8 is selected from pyridyl, thienyl, thiazolyl, oxazolyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolinyl, imidazolyl, and benzimidazolyl, wherein R^8 is optionally substituted at a substitutable position with one or more substituents independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, propoxy, butoxy, isobutoxy, pentoxy, methylthio, amino, N-methylamino and N,N-dimethylamino; or a pharmaceutically-acceptable salt thereof.

12. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 1; or a pharmaceutically-acceptable salt thereof.

13. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 2; or a pharmaceutically-acceptable salt thereof.

14. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 3; or a pharmaceutically-acceptable salt thereof.

15. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 4; or a pharmaceutically-acceptable salt thereof.

16. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 5; or a pharmaceutically-acceptable salt thereof.

17. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 6; or a pharmaceutically-acceptable salt thereof.

18. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 7; or a pharmaceutically-acceptable salt thereof.

19. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said

compound selected from a family of compounds of Claim 8; or a pharmaceutically-acceptable salt thereof.

20. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 9; or a pharmaceutically-acceptable salt thereof.

21. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 10; or a pharmaceutically-acceptable salt thereof.

22. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 11; or a pharmaceutically-acceptable salt thereof.

23. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 1; or a pharmaceutically-acceptable salt thereof.

24. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 2; or a pharmaceutically-acceptable salt thereof.

25. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 3; or a pharmaceutically-acceptable salt thereof.

26. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 4; or a pharmaceutically-acceptable salt thereof.

27. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 5; or a pharmaceutically-acceptable salt thereof.

28. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 6; or a pharmaceutically-acceptable salt thereof.

29. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 7; or a pharmaceutically-acceptable salt thereof.

30. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 8; or a pharmaceutically-acceptable salt thereof.

31. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having

or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 9; or a pharmaceutically-acceptable salt thereof.

32. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 10; or a pharmaceutically-acceptable salt thereof.

33. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 11; or a pharmaceutically-acceptable salt thereof.

34. The method of Claim 23 for use in treatment of inflammation.

35. The method of Claim 23 for use in treatment of an inflammation-associated disorder.

36. The method of Claim 35 wherein the inflammation-associated disorder is arthritis.

37. The method of Claim 35 wherein the inflammation-associated disorder is pain.

38. The method of Claim 35 wherein the inflammation-associated disorder is fever.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/09444

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/26 A61K31/425 C07D417/04 C07D417/12 C07D277/56
C07D277/30 C07D277/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 513 387 (OTSUKA PHARMACEUTICAL CO.LTD) 19 November 1992 see page 116,compound of example 45 see claims	1-38
X	US,A,4 632 930 (DAVID J.CARINI ET AL) 30 December 1986 cited in the application see column 13 - column 20; claims; examples 29-43	1,12-22
X	FR,M,8 018 (JOHN WYEETH AND BROTHER LIMITED) 3 August 1970 see abstractand page 1 last paragraph	1,12-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 October 1995	17. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

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INTERNATIONAL SEARCH REPORT

Inter ional Application No
PCT/US 95/09444

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 55, no. 24, 27 November 1961 Columbus, Ohio, US; abstract no. 24721b, L.M.YAKUPOLSKI ET AL 'Synthesis of some derivatives of phenyl trifluoromethyl sulfide and phenyl trifluoromethyl sulfone' see abstract & ZHUR.OBSHCHEI KHIM., vol. 31, 1961 pages 1315-1320, ---	1-11
X	CHEMICAL ABSTRACTS, vol. 118, no. 3, 18 January 1993 Columbus, Ohio, US; abstract no. 22226k, page 692; see abstract & JP,A,04 244 073 (FUJISAWA PHARMACEUTICAL CO.,LTD) 1 September 1992 ---	1,12-22
A	GB,A,2 022 085 (PFIZER INC) 12 December 1979 see the whole document ---	1-38
A	EP,A,0 149 884 (TAKEDA CHEMICAL INDUSTRIES LTD) 31 July 1985 see page 37 - page 39; claims ---	1-38
P,X	WO,A,95 00501 (MERCK FROSST CANADA INC.) 5 January 1995 cited in the application see claims ---	1-38
P,X	INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 56, no. 5, September 1994 BOMBAY, pages 192-195, T.ARULMODI ET AL 'Synthesis and antibacterial activity of 2-substituted benzyl-4-(p-phenylsulfonamido)-5-unsubstit uted/methylthiazoles' see the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US95/09444

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 23-38 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter[illegible]nal Application No
PCT/US 95/09444

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/09444

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